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VOL. LXII, No. 3 NEW SERIES JUNE 1955

THE OVARIAN THECA CELL

Part IV—The Hyperthecosis Syndrome

BY

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Nothing can happen without a cause.
Polybius

In 1935 Stein and Leventhal first demonstrated by means of ovarian wedge resection the apparent cure of a condition consisting of bilateral polycystic ovaries associated with secondary amenorrhoea, sterility and often masculinization. Since then a number of papers have appeared confirming these observations (Bailey, 1937; Stein and Cohen, 1939; Leventhal, 1941; Geist and Gaines, 1942; Stein, 1945; Reycraft, 1949; Stein, Cohen and Elson, 1949; Ingersoll and McDermott, 1950).

Although most of the above authors must have observed in their clinics that bilateral polycystic ovaries were often associated with uterine bleeding and hyperplastic endometria, rather than amenorrhoea and masculinization, no attempt was made except by Robinson (1935) to discuss or describe the former features in their papers, or to venture an explanation for this apparent paradox. Nor was any attempt made to interpret the hirsutism and masculinizing manifestations. The increase of thecal activity in the ovaries in this condition had been observed by many of these authors but since "the theca cells as well as the granulosa cells are estrin producing" (Stein and Cohen, 1939) this feature went unheeded.

It was not until 1949, when Culiner and Shippel first presented evidence to suggest that the probable function of the theca cell was that of an androgen producer, that any attempt was made to explain the masculinizing features of this condition. Since then the probable androgenic function of the theca cell has been studied in great detail (Shippel, 1950a, b, c).

Only recently Leventhal and Cohen (1951), although at first apparently agreeing with the observations of Culiner and Shippel concerning the probable androgenic function of the theca cell, ultimately came to the conclusion that, because the theca cells in this condition are often luteinized and there is usually a high pregnanediol urine excretion in these cases, the cause of the masculinization could also possibly be due to progesterone. Although superficially this concept may seem plausible, experimentally it has not been possible to show that progesterone possesses such androgenic propensities as to cause hirsutism and marked masculinization. No case of persistent functional corpus luteum has ever been known to be associated with masculinization (Black, Heyns and Gillman, 1941; Selye, 1947; Novak, 1952). Evidence has already been presented in a previous paper (Shippel, 1950b, p. 379) to show that at the present stage of our knowledge it is most precarious to assume that the presence of pregnanediol in the urine necessarily indicates only progesterone activity. As regards the frequent luteinization of the theca cell in this condition it is most unfortunate that luteinization of a cell has come to be blindly accepted as signifying progesterone activity. Although it is true that the cells of the corpus luteum which produce progesterone are luteinized there is absolutely no proof that the reverse is necessarily

true. Novak (1952) mentions the fact that in most cases of luteinized ovarian tumours the endometrium fails to show progesterone effects. The derivation of the word "luteinize" is from the Latin word "luteus" meaning yellow and the word corpus luteum simply means yellow body and not producer of progesterone. We have, therefore, no right to assume that because a specific yellow structure, yellow because of the presence of fat in its cells, is a source of progesterone, that all yellow cells, i.e., luteinized cells, are also necessarily a source of this hormone. This false assumption it is felt has rather hindered than enhanced our studies of the ovarian endocrinological functions.

The aetiology of bilateral polycystic ovaries has invariably been sought in the pituitary, it being felt that the "ovarian dysfunction is most often only an ovarian reflection of disordered function of the anterior pituitary" (Novak, 1949). This disordered pituitary function it was felt resulted in marked activity and crowding together of follicles in the ovary, and in some mysterious manner also accounted for the thickening and fibrosis of the tunica, with the consequent development of a "mechanical blockade" (Leventhal, 1941) making ovulation impossible. It was in order to alleviate this mechanical barrier that the operation of wedge resection was devised; an operation which, if the primary aetiological factor is an abnormal pituitary, is most illogical. It is probably this illogicality which has made this operation most unpopular amongst the majority of gynaecologists. Yet paradoxically enough Stein and his colleagues, who have followed up their cases for more than 15 years, have failed to observe a single recurrence of this condition in over 75 cases (Stein, Cohen and Elson, 1949).

It was in order to elucidate this strange paradox that it was decided, on the basis of previous observations (Shippel, 1950a, b) to study the ovaries critically, and to observe whether any correlation existed quantitatively between the thecal and granulosal elements of the ovary, and the associated endometrial and symptomatological patterns. The results of this study have proved far more fruitful than was originally thought possible. The object of this paper is, therefore, not to present a further series of cases confirming the observations of all the above authors, but rather to attempt an explanation of the above paradox on the basis of this study, and to come to a logical conclusion regarding the aetiology and pathogenesis of this hyperthecosis syndrome. It is further hoped to show (*a*) that the syndrome of secondary amenorrhoea, hirsutism and masculinization as first described by Stein and Leventhal (1935) is merely the end result of a very much larger syndrome; (*b*) that the many conditions associated with menorrhagia, endometrial hyperplasia, and cystic glandular hyperplasia which are today considered as separate entities, are merely phases of this syndrome and (*c*) to present further evidence of the androgenic function of the theca cell.

Material

The material of 37 cases utilized for this study has been collected, except for 2 cases, over the past 2 years. This fact proves that the condition of hyperthecosis ovarii is a relatively common disease provided it is recognized in its earlier stages. Only 6 of these cases presented with all the symptoms which according to Stein and Leventhal (1935) and all the following authors (Bailey, 1937; Stein and Cohen, 1939; Leventhal, 1941; Geist and Gaines, 1942; Stein, 1945; Reycraft, 1949; Stein, Cohen and Elson, 1949; and Ingersoll and McDermott, 1950) are necessary for the diagnosis of this condition, namely, amenorrhoea, sterility, hirsutism and masculinization. These 6 cases were collected over the past 4 years; a figure which is in accordance with the observations of the above authors. It will thus be seen that the fully developed condition is, as these authors state, rather rare.

The specimens as received at our gynaecological pathology laboratory from various hospitals, and gynaecologists in private practice over whom we have obviously no control regarding the type of operation performed, consisted of total or subtotal hysterectomies plus bilateral salpingo-oöphorectomies, or ovarian wedge resections with or without endometria removed by diagnostic curettage. The wedge resections in the large majority of cases were performed according to the technique described by Stein (1945). In a number of these

cases 17-ketosteroid estimations were done prior to the operation.

The disadvantage associated with the hysterectomy cases in that they made follow-up regarding the menstrual cycles impossible was far outweighed by the availability of valuable material for study. In any case the follow-up of cases suffering from this condition has been carried out by Stein and his colleagues so efficiently and for so many years as to make a follow-up in the above hysterectomy cases relatively unimportant.

All the ovaries exhibited the typical thickened tunica and on bisection large numbers of micro- and occasional cystic-follicles. At least 3–4 sections were taken from various areas of each ovary, and, if the uterus was available, endometrium plus a portion of uterine wall from 3 to 4 different sites.

Some of these sections were stained for fat with Scharlach R and the rest with haematoxylin and eosin. When necessary special techniques were used such as silver impregnation stains for reticulum.

Classification

Notwithstanding the fact that the recording of the histories and pathological findings of each of the 37 cases studied would result in a very lengthy presentation, it is felt that this step is necessary if the progressive stages in the development of this very broad disease entity are to be adequately demonstrated, and the integration of many syndromes today considered separate entities accomplished.

These cases have been arranged according to the degree of deviation from the normal commencing with the least abnormal, and, for the sake of clarity, have been classified under 6 principal headings according to the thecal-granulosal ratios. Appended to each heading are summaries of the cardinal ovarian and endometrial patterns. These groups are further subdivided according to the main presenting symptoms. It will thus be possible to see, (*a*) the progressive stages in the development of this syndrome; (*b*) how close a correlation there exists between the ovarian thecal-granulosal ratios and the endometrial patterns, and (*c*) how wide and varied can be the symptomatology.

Two terms which require definition, since they occur frequently in the ovarian pathological reports, are prothecal and non-cystic follicles. By the former term is meant the modified stromal cells which often occur in relationship to ovarian follicles in this condition. They usually exhibit active mitosis, are bloated and stain very much less deeply than the normal stromal cell. It is felt that they are precursors of the theca cell. They were not taken into consideration in the assessment of the thecal-granulosal ratios of each case, however, since it is doubtful whether at this stage of development they have any hormonic function. By the latter term is meant those follicles which are either in the early stages of regression or are beginning to become cystic.

Case Reports

Group 1. The Early Thecal-Granulosal Synergistic Phase

Characteristic Ovarian Microscopical Patterns: The characteristic features of the ovaries at this stage are their polycystic nature, somewhat thickened tunica, cellular stroma, follicles at all stages of development, normal amounts of theca and granulosa in developing and non-cystic follicles and only slight to nil in cystic and atretic follicles, and commencing prothecal development. Except for the areas of prothecal development around a number of follicles there is thus at this stage no appreciable deviation of the follicles from the normal. However, the sum total of their thecal-granulosal activity is probably somewhat greater than the normal.

Characteristic Endometrial Microscopical Patterns: The characteristic features of the endometrium at this stage are a proliferative pattern with active mitosis of both the gland and stromal cells, and a tendency towards crowding of glands, glandular inclusions and pseudo or true stratification of gland cells.

Main Symptoms: (i) *Hirsutism and cyclical bleeding; the intermenstrual interval is, however, becoming greater and the amount of bleeding increased*

Case 1. G.5264, S.I., aged 20 years, married 2 months, gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 22nd February, 1952.

Main Complaints. Increasing hirsutism for the past 8 years, excessive bleeding at the menses, and spasmodic dysmenorrhoea.

Menarche unknown. The menses were always regular being 5–6/35 until 6 months ago when they changed to 10/42–50.

General examination. Although the hair distribution was masculine in type the configuration was feminine.

Pelvic Examination. The external genitalia were normal but the vagina was septate. Both ovaries were hard and enlarged particularly the left which was the size of a golf ball.

Operation. 21st May, 1952. At laparotomy a uterus bicornis duplex was found. A plastic operation to the uterus making it a single organ and a bilateral ovarian wedge resection was performed. The left ovary, in addition to the sclerocystic element, was the site of a dermoid cyst.

Microscopical findings of ovaries. Sections of both ovaries exhibit moderately thickened tunicae, a number of primordial and cystic follicles (Fig. 1), some non-cystic and developing follicles, and a few atretic follicles. Most of the cystic follicles exhibit only slight thecal-granulosal activity, both these layers being no more than 2 to 3 cell-layers thick. In the non-cystic and developing follicles, on the other hand, these cell elements are present in normal amounts. The atretic follicles exhibit either very slight or no thecal activity. Fair amounts of protheca occur around some of the above follicles (Fig. 2).

Conclusion. The pattern exhibited by these ovaries is that of an hyperthecosis ovarii in the early thecal-granulosal synergistic phase.

Progress. 24th March, 1953. The patient bled for 3 weeks in June, 1952. Since then the menses have been perfectly regular, the periodicity being 5/28.

Case 2. B.450. F.J.L., aged 24 years, married 3 months, gravida-0, was first seen at the Bloemfontein National Hospital on the 6th June, 1952.

Main Complaints. Hirsutism and frigidity for 4 years, and excessive bleeding at the menses the intermenstrual interval of which has increased.

Menarche at 13 years. The menses were always regular, being 7/28 until 4 years ago, when they changed to 10/35.

General examination. Except for a moderate degree of hirsutism of the face, trunk and extremities and a male type of pubic escutcheon, nil abnormal was detected.

Pelvic examination. The genitalia were normal except for a slight enlargement of both ovaries particularly the left.

Operation. 10th June, 1952. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit moderately thick tunicae, a moderate number of primordial follicles, some non-cystic, developing and cystic follicles, one collapsed follicle and around a number of follicles some areas of protheca. Both the theca and granulosa are completely atrophic in some of the cystic follicles, whilst in others only a slight amount of theca is present—1 to 2 rows in thickness. The amount of theca and granulosa in the non-cystic and developing follicles is within normal limits. Only in the collapsed follicle is the granulosal and thecal activity fair in amount as evidenced by the thickness and mitotic activity of both groups of cells.

Conclusion. The pattern exhibited by these ovaries is that of an hyperthecosis ovarii in the early thecal-granulosal synergistic phase.

Progress. 22nd December, 1952. The periods are now perfectly regular and the periodicity 6/28. There is improvement in the hirsutism and the libido is normal.

Main symptoms: (ii) *Irregular Menses*

Case 3. B.323, M.M.O., aged 49 years, widow for 16 years, para-4 and gravida-4, was first seen at the Johannesburg General Hospital on the 5th December, 1951.

Main Complaint. Irregular menses with marked bleeding and dysmenorrhoea for the last 5 years.

Menarche at 11 years. The menses were always more or less regular, being 11 days/$\pm$1 month until 5 years ago, when they changed to 9-12 days/irregular.

General examination. Except for some stoutness nil abnormal was detected. There was no evidence of hirsutism.

Pelvic examination. The external genitalia were normal. The uterus appeared to be a little smaller than normal. A large, hard and immobile mass, extending up to the umbilicus, was felt through the posterior fornix. The cervix was displaced anteriorly beneath the symphysis pubis.

Operation. 7th December, 1951. At operation a large whitish mass with a smooth capsule measuring $\pm 6 \times 5 \times$ 4 inches was found in the left adnexal region. A total hysterectomy plus bilateral salpingo-oöphorectomy was performed.

Microscopical findings. (a) *Ovaries:* The left ovarian tumour exhibits the typical pattern of a fibromyoma. The right ovary shows the presence of a somewhat thickened tunica and a few non-cystic and developing follicles which exhibit only slight to normal amounts of thecal and granulosal activity. The occasional cystic follicle present shows no activity. A degenerating corpus luteum is present in the one ovary.

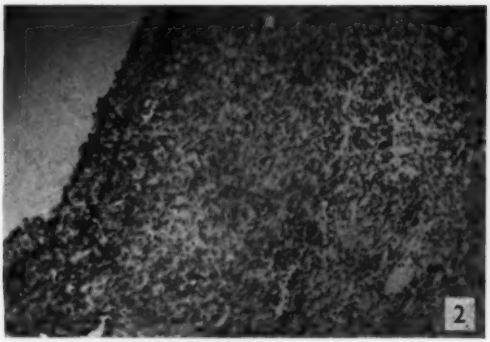
(b) *Endometrium:* The endometrium shows a proliferative pattern. The glands are tubular and in parts are crowded together. Many of these glands exhibit a moderate degree of pseudostratification (Fig. 3). The stroma is rather oedematous. Very active mitosis is present in both the glands and stroma.

Conclusion. The patterns exhibited by the ovaries and endometrium are those of a case of hyperthecosis ovarii in the early thecal-granulosal synergistic phase.

Case 4. B.472, J.W., aged 34 years, married, para-2, gravida-3, was first seen at the Johannesburg General Hospital on the 23rd June, 1952.

Main Complaints. Severe attacks of lower abdominal pain which have no relationship to the menstrual period, irregularity of the menses and complete loss of libido.

Menarche at 12 years. The menses were always



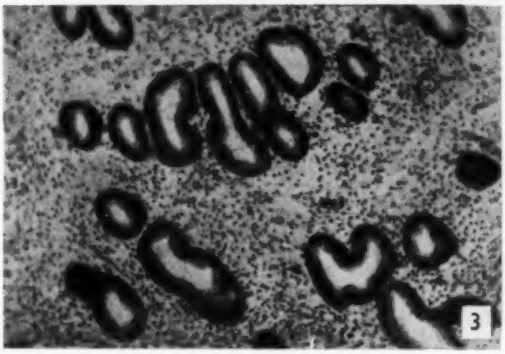


FIG. 1

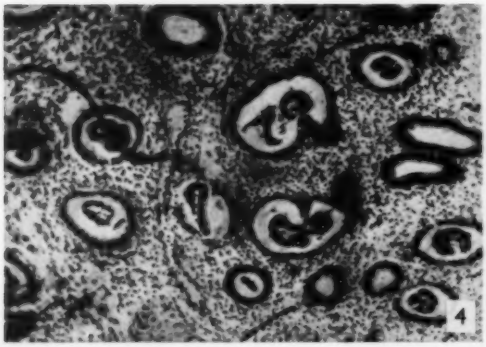
Case 1. Section of ovary showing a number of cystic follicles. ×22.

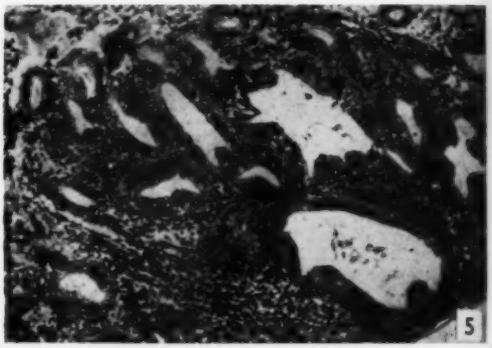
FIG. 2

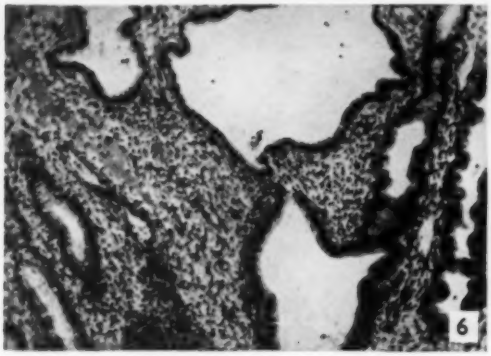
Case 1. Section of ovary showing a follicle with some granulosa, theca and a broad zone of protheca. ×90.

FIG. 3

Case 3. Section of endometrium showing pseudostratification of the gland cells and a tendency towards crowding of the glands. ×90.







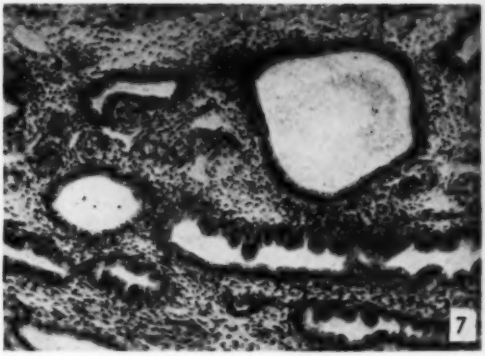


FIG. 4

Case 6. Section of endometrium showing glandular intussusception and a slight cystic tendency of some glands. (Slide unfortunately cracked.) ×90.

FIG. 5

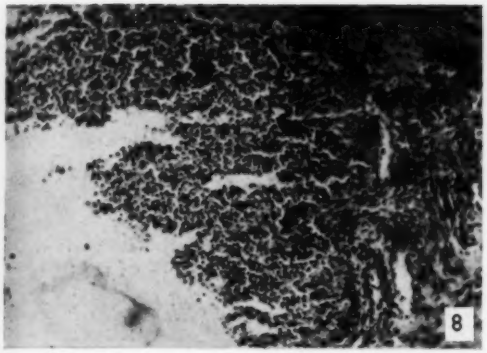
Case 8. Section of endometrium simulating adenocarcinoma because of marked crowding of glands, pseudostratification of cells and cystic tendency of some glands. ×90.

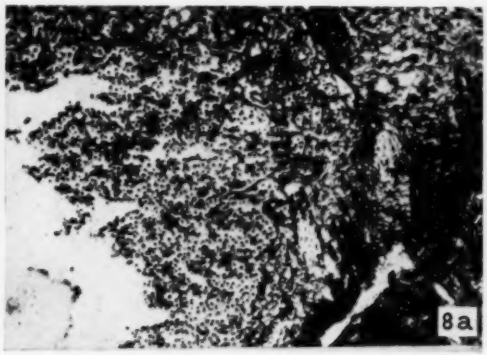
FIG. 6

Case 30. Section of endometrium showing a few cystic glands and some degree of pseudostratification of their cells. ×90.

FIG. 7

Case 30. Another area of the endometrium depicted in Fig. 6 to show tendency towards pseudostratification of the cells and a cystic tendency of some glands. ×90.





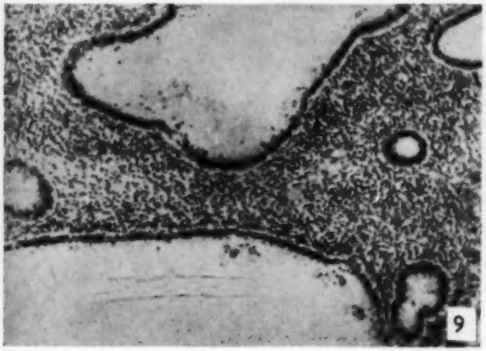


FIG. 8

Case 6. Section of ovary showing an area of marked granulosal and some thecal activity. (See Fig. 8a.) ×90.

FIG. 8a

Case 6. Section of ovary through same area as depicted in Fig. 8 but stained for reticulum to differentiate between the granulosa and theca; the thecal element being that portion closely related to the reticulum. ×90.

FIG. 9

Case 6. Section of endometrium showing a typical Swiss-cheese pattern, cf. Fig. 4. ×90.

FIG. 10

Case 14. Section of endometrium showing a typical Swiss-cheese pattern. ×90.

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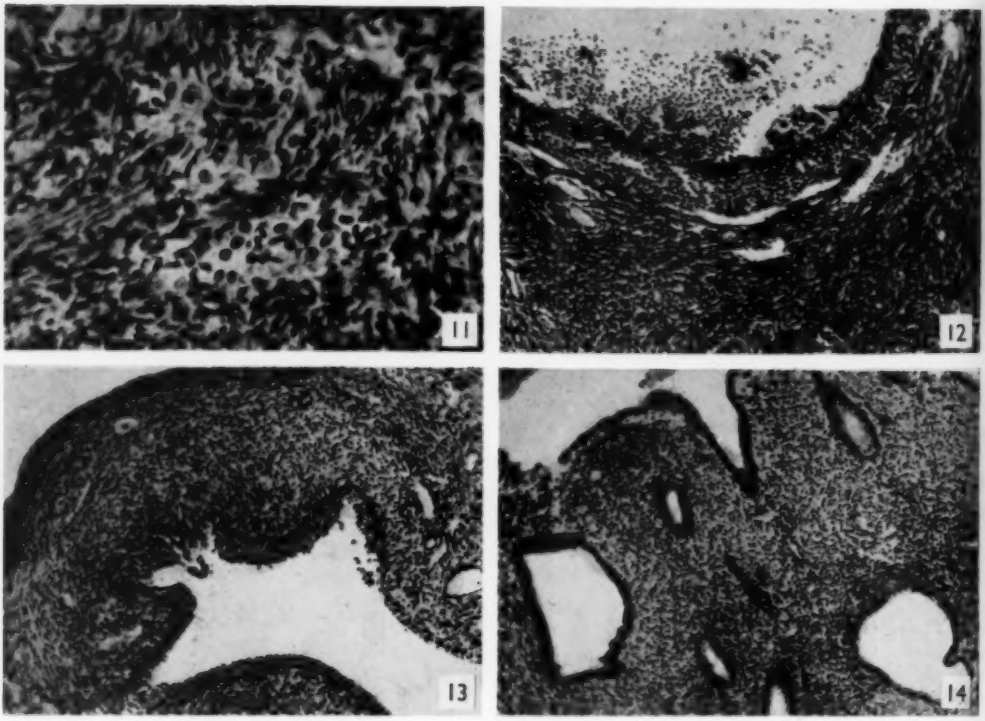


FIG. 11

Case 8. Section of ovary exhibiting a number of small islands of theca cells scattered throughout the stroma. ×360.

FIG. 12

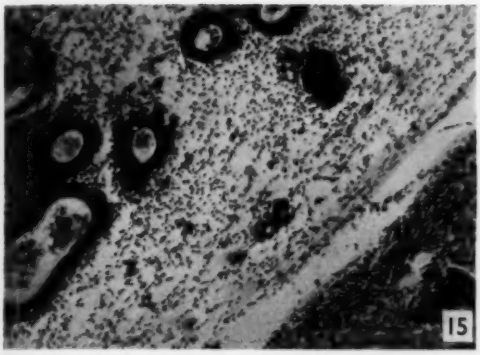
Case 8. Section of ovary showing a follicle undergoing atresia and exhibiting a normal amount of thecal activity. ×90.

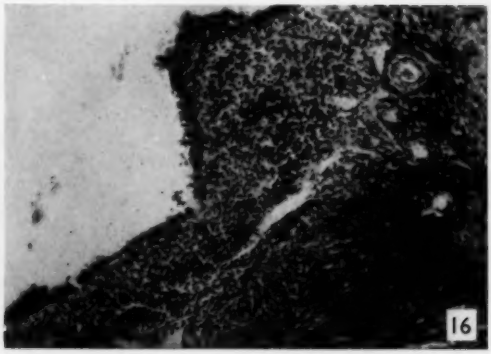
FIG. 13

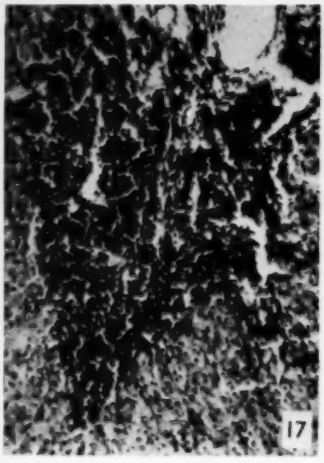
Case 14. Section of ovary showing a follicle undergoing atresia and exhibiting a moderate amount of thecal activity; ? on verge of intermediate thecal dominant phase. ×90.

FIG. 14

Case 14. Section of endometrium, which is becoming attenuated, still showing a few slightly cystic glands. cf. Fig. 10. ×90.







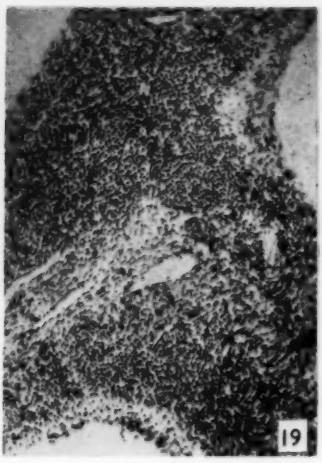


FIG. 15

Case 15. Section of ovary showing an area of endometriosis. ×90.

FIG. 16

Case 15. Section of ovary showing a follicle undergoing atresia and exhibiting a moderate amount of thecal activity. ×90.

FIG. 17

Case 15. Section of ovary showing a corpus luteum exhibiting a large zone of paralutein tissue. ×90.

FIG. 18

Case 16. Section of endometrium with a paucity of mitotic figures showing an occasional cystic gland. ×90.

FIG. 19

Case 16. Section of ovary showing a number of atretic follicles exhibiting moderately thick zones of thecal activity. ×90.

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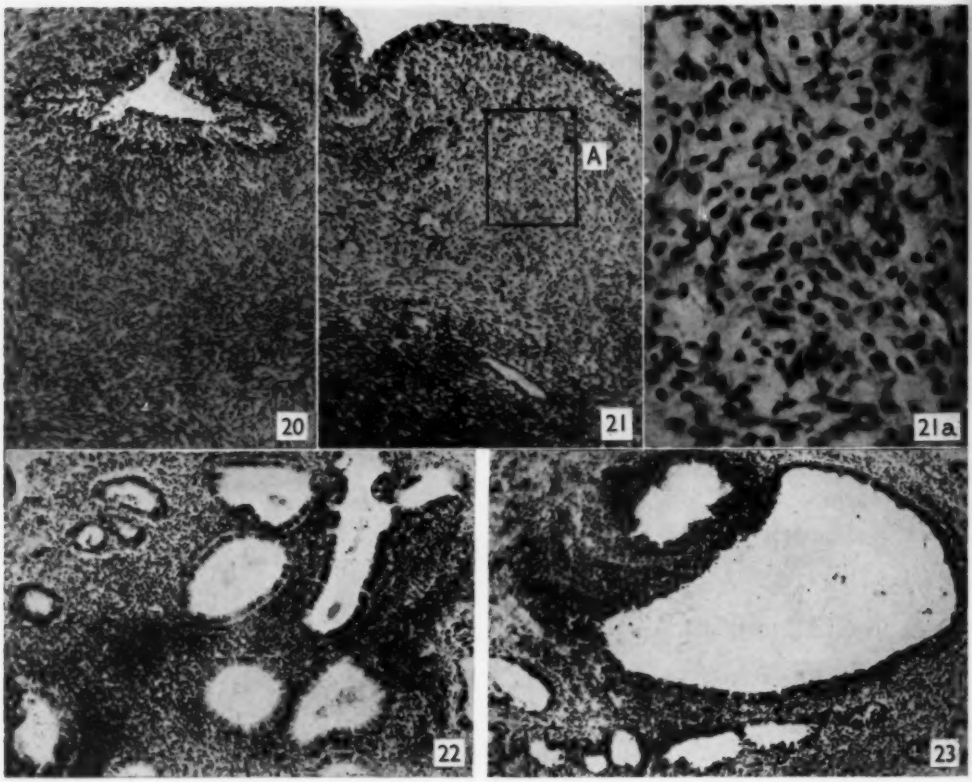


FIG. 20

Case 16. Section of ovary showing a collapsed follicle which is beginning to undergo atresia, exhibiting a moderately thick zone of luteinized theca cells and an area of protheca. ×90.

FIG. 21

Case 16. Section of ovary showing a follicle which is undergoing atresia and exhibiting a broad zone of prothecal activity. ×90.

FIG. 21a

Case 16. High power detail of area A Fig. 21 to show mitotic activity in prothecal zone. ×360.

FIG. 22

Case 18. Section of endometrium with a paucity of mitotic figures showing glands which are still slightly cystic. ×90.

FIG. 23

Case 18. Another area of the endometrium depicted in Fig. 22 to show the persistence of the occasional grossly cystic gland. ×90.

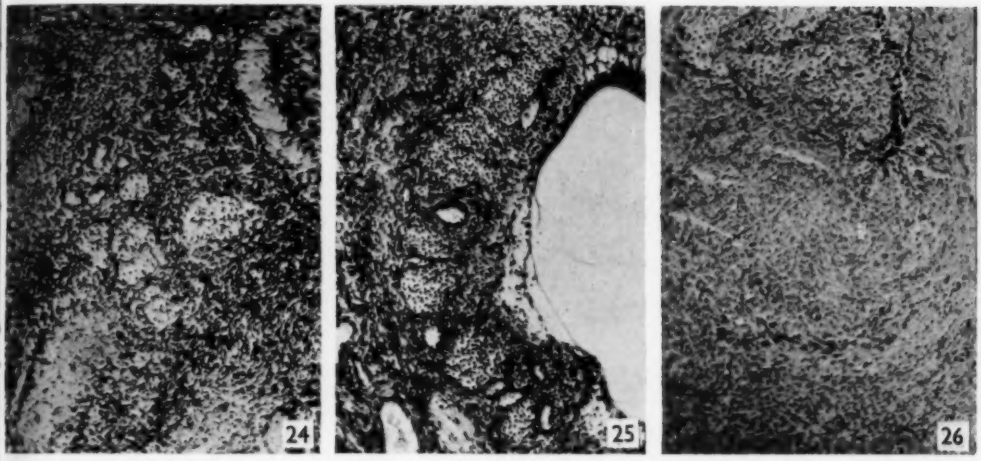


FIG. 24

Case 18. Section of ovary exhibiting a number of small islands of theca cells scattered throughout the stroma. ×90.

FIG. 25

Case 18. Section of ovary showing an atretic follicle with a moderately broad zone of luteinized theca cells which resemble those of the adrenal gland. ×90.

FIG. 26

Case 18. Section of ovary showing a follicle undergoing atresia and exhibiting some luteinized granulosa and theca cells and a very broad zone of protheca. ×90.

GROUP 6. LATE THECAL DOMINANT PHASE. TYPE I

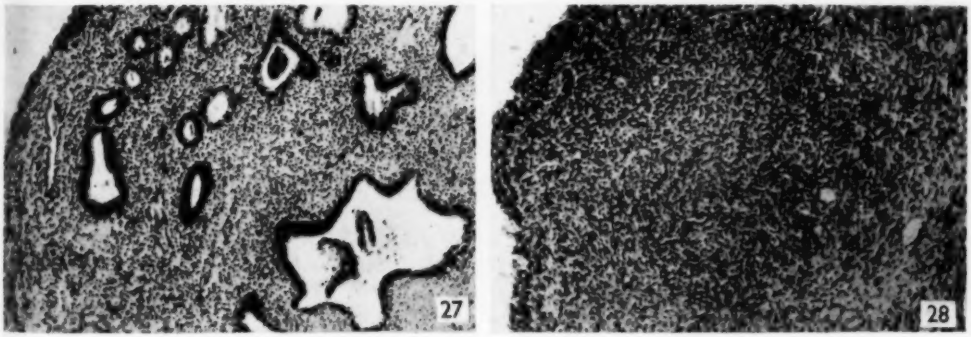
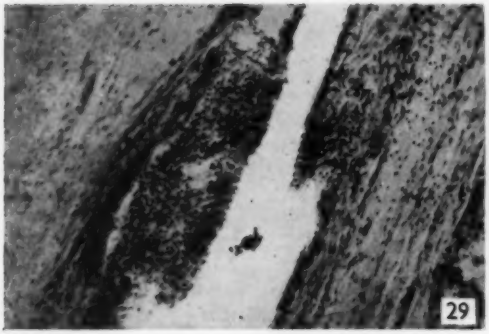


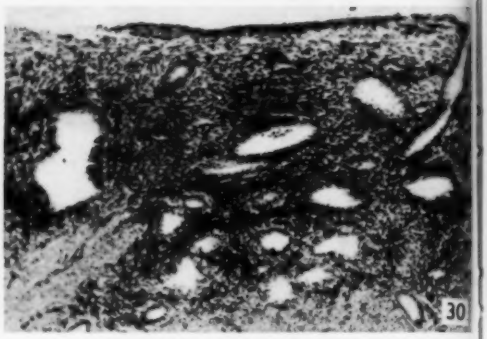
FIG. 27

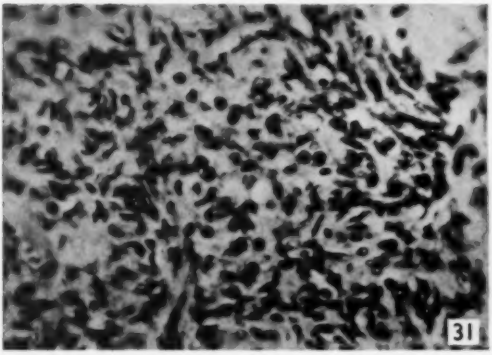
Case 21. Section of endometrium with a marked paucity of mitotic figures showing the occasional cystic gland and glandular inclusion. ×90.

FIG. 28

Case 21. Section of ovary showing a follicle undergoing atresia and exhibiting marked thecal activity. ×90.







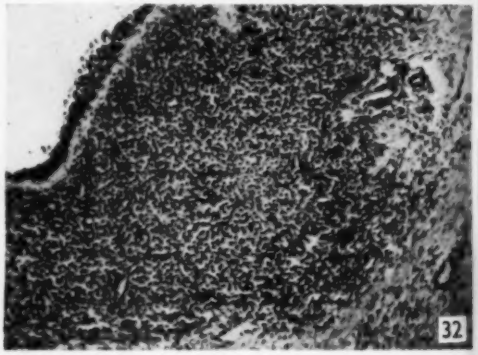


FIG. 29

Case 30. (See case report.) Section of ovary showing patchy thickening of thecal zone in an atretic follicle. ×90.

FIG. 30

Case 30. Section of endometrium showing complete atrophy. cf. Figs. 6 and 7. ×90.

FIG. 31

Case 33. Section of ovary showing large islands of theca cells, many of which are luteinized. ×360.

FIG. 32

Case 33. Section of ovary showing an atretic follicle with marked thecal activity. ×90.

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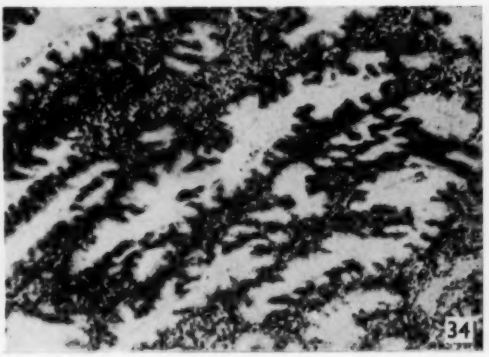


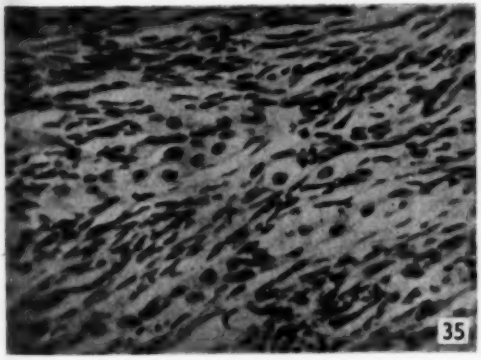
FIG. 33

Case 33. Another zone of ovary depicted in Fig. 32 to show areas undergoing hyalinization. A similar pattern was observed in the ovaries of Case 25. ×90.

FIG. 34

Case 33. Section of endometrium, removed a few months following ovarian wedge resection, showing a very good secretory pattern. ×90.

GROUP 6. LATE THECAL DOMINANT PHASE. TYPE 3



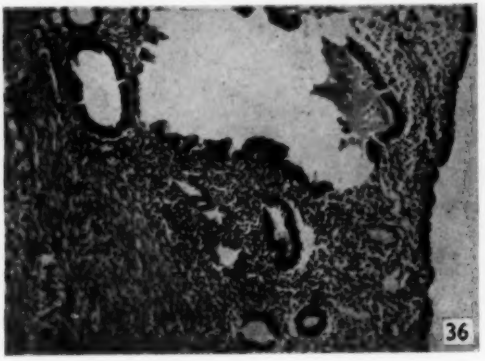
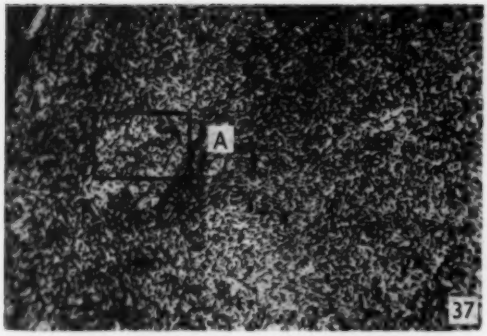


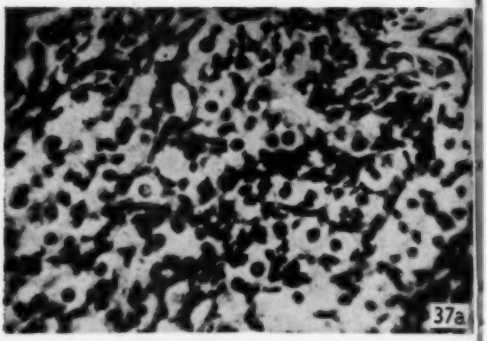
FIG. 35

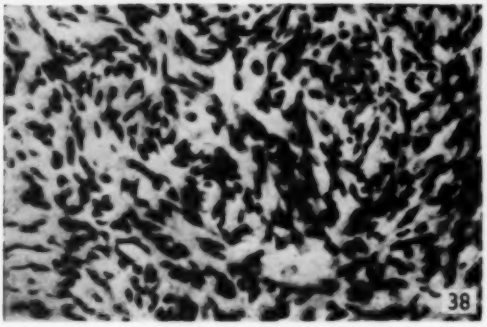
Case 35. Section of ovary showing islands of theca cells scattered throughout the stroma. Follicles are no longer observable. ×360.

FIG. 36

Case 35. Section of endometrium which is completely atrophic exhibiting cystic glands. ×90.







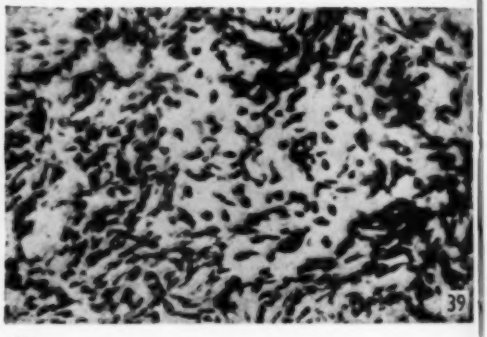


FIG. 37

Case 36. Section of ovary consisting only of thecal islands and stroma, follicles no longer being observable. ×100.

FIG. 37a

Case 36. High power of detail of area A, Fig. 37, to show marked luteinization of the theca cells. ×400.

FIG. 38

Case 36. Section of ovary showing the evolution of theca cells from the stroma. ×400.

FIG. 39

Case 36. Section of ovary showing the regression of theca cells to the stroma. ×400.

THECA CELL TUMOUR

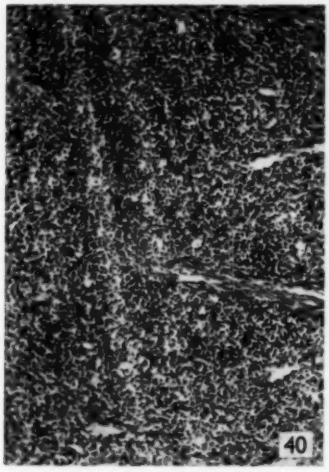


FIG. 40

Case 37. Section of ovarian tumour showing the typical pattern of a thecoma. ×90.

OVARIAN THECAL RESPONSE IN PREGNANCY

FIG. 41

Section of ovarian biopsy removed at Caesarean section showing marked thecal response around an atretic follicle. ×90.

FIG. 42

Section of ovary, removed post-mortem from a patient dying soon after delivery, showing a similar pattern to that of Fig. 41. ×90.

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regular, being 3–4/30 days until 15 months ago, when they became 3–10/15–30 days.

Obstetrical History. Para-2, gravida-3. A few weeks following the birth of her last child in 1948 the patient had a severe haemorrhage which persisted for a number of weeks. Because of this she breast fed the infant for only about a month.

General examination. Nil abnormal was detected. There was no evidence of hirsutism.

Pelvic examination. The external genitalia and uterus were normal. Through the right fornix a tense, cystic, mobile, tender mass was felt, apparently not attached to the uterus or cervix. This mass appeared to be 3–3½ inches in diameter.

Operation. 26th June, 1952. An ovariotomy of the ovarian cyst and wedge resection of the left ovary was performed. The right ovarian cyst exhibited the typical pattern of a unilocular pseudo-mucinous cystadenoma. At one pole there was still some ovarian tissue present. The left ovary was rather large.

Microscopical findings. (a) *Ovaries:* Sections of the former ovarian tissue and of the wedge of the left ovary exhibit a thickened tunica, a cellular stroma, a number of non-cystic and cystic follicles, a few atretic follicles with a small amount of thecal activity, and in each ovary a single corpus thecale. The large majority of follicles are non-cystic and exhibit normal amounts of both theca and granulosa cells; both these cellular elements showing fairly marked mitotic activity. Prothecal elements, moderately thick in parts, are present around a number of follicles.

(b) *Endometrium:* The large majority of glands are tubular, many containing glandular epithelium in their lumina. Most of the gland cells exhibit active mitosis and a moderate degree of pseudostratification.

Conclusion. The patterns exhibited by the ovaries and endometrium are those of an hyperthecosis ovarii in the early thecal-granulosal synergistic phase.

Progress. 26th November, 1952. The menses are now quite regular and the libido normal.

Group 2. The Intermediate Thecal-Granulosal Synergistic Phase

Characteristic Ovarian Microscopical Patterns: There is very little observable difference between the ovarian patterns of this phase and those of the previous phase. The main difference is in the endometrium.

Characteristic Endometrial Microscopical Patterns: In addition to the endometrial patterns observed in the previous phase some of the glands now show a cystic tendency and occasionally some are even cystic.

Main Symptoms: Menorrhagia

Case 5. B.394, L.M., aged 45 years, married, gravida-4, para-4, was first seen at the Coronation Non-European Hospital on the 10th April, 1952.

Main Complaint. More or less continuous vaginal bleeding for the past 2 months.

Menarche unknown. The menses were always regular being 4/30 days until recently when they became somewhat irregular.

General examination. Except for a slight pallor nil abnormal was detected. There was no evidence of hirsutism.

Pelvic examination. The uterus was enlarged to the size of approximately a 14-weeks pregnancy. It was firm and irregular, suggestive of the presence of myomata.

Operation. 16th April, 1952. At operation a myoma the size of a fowl's egg was found situated on the fundus. A total hysterectomy plus bilateral salpingo-oöphorectomy was performed.

Microscopical findings. (a) *Ovaries:* Sections of both ovaries exhibit a number of non-cystic and developing follicles, some cystic follicles, only a very occasional atretic follicle and, in parts, moderately thick zones of protheca. The non-cystic and developing follicles show a degree of thecal-granulosal activity which is within normal limits. In the cystic follicles both these layers of cells are atrophic. In the occasional atretic follicle the degree of thecal activity is within normal limits.

(b) *Endometrium:* The endometrium is thick. Except for a few very cystic glands the large majority of glands are tubular. The cells in these latter glands show rather marked pseudostratification and very active mitosis. The stroma is compact.

Conclusion. The patterns exhibited by these ovaries and endometrium are suggestive of this being a case of hyperthecosis ovarii in the intermediate thecal-granulosal synergistic phase.

Group 3. The Late Thecal-Granulosal Synergistic Phase

Characteristic Ovarian Microscopical Patterns: The characteristic features of the ovaries at this stage are their polycystic nature, thickened tunica, cellular stroma, prothecal activity, follicles at all stages of development *with usually rather marked thecal-granulosal activity in some non-cystic follicles* and only slight to nil in cystic and atretic follicles. On occasions, however, the amount of follicular thecal-granulosal activity may not be much greater than that found in the previous phases. There is usually, though, a history of fairly prolonged amenorrhoea in these latter cases, suggesting thereby that the endometrium has been given time to assume its hyperplastic features.

Characteristic Endometrial Microscopical Patterns: The endometrium at this stage exhibits a typical swiss-cheese pattern with active mitosis of both gland and stromal cells.

Main Symptoms: Menorrhagia

Case 6. B.381 and 381(a). J.M.T., aged 49 years, married, para-1 and gravida-1, was first seen at the Johannesburg General Hospital on the 1st April, 1952.

Main Complaint. Continuous vaginal bleeding for the 3-months period between December, 1951 and 9th March, 1952 preceded by an episode of 2-months amenorrhoea.

Menarche at 14 years. The menses were always regular being 4/21 days until 1951 when they became irregular.

General examination. Nil abnormal was detected.

Pelvic examination. The cervix was soft and bulky and the uterus enlarged to the size of an 8-weeks pregnancy.

Operation. 3rd April, 1952. A diagnostic curettage was done.

Microscopical findings of the endometrium. The endometrium shows a varied glandular pattern. In areas the glands are crowded together. Quite a large number contain glandular epithelium in their lumina and a few show a cystic tendency (Fig. 4). A feature common to all these glands, no matter their shape, is the moderate to marked degree of pseudostratification of their cells. The stromal cells are moderately well differentiated in patches. Active mitosis is present in both the gland and stromal cells.

Conclusion. The varied gland patterns and the cystic tendency of some of the glands suggest that this is a case of hyperthecosis ovarii in the intermediate thecal-granulosal synergistic phase.

In view of the patient's age and the above findings she was operated upon again on the 9th June, 1952.

Operation. 9th June, 1952. A total hysterectomy plus bilateral salpingo-oöphorectomy was done. Both ovaries were enlarged, polycystic, and exhibited thickened tunicae. The endometrium was more than 5 mm. thick.

Microscopical findings. (a) *Ovaries:* Notwithstanding the patient's age the odd primordial follicle is still present in the cortex. Both ovaries exhibit large, somewhat collapsed follicles with marked granulosal and thecal activity, the thecal element being present in a somewhat smaller amount than the granulosa (Figs. 8 and 8a). Active mitosis is present in both groups of cells.

(b) *Endometrium:* The endometrium now exhibits a typical swiss-cheese pattern (Fig. 9); the majority of the glands showing some degree of pseudostratification.

Conclusion. The marked granulosal-thecal activity of the ovaries and the cystic glandular hyperplastic state of the endometrium suggest that this is a case of hyperthecosis ovarii in the late thecal-granulosal synergistic phase. It is important to note the progressive changes that have occurred in the endometrium over a period of 2 months.

Case 7. B.330. J.P.B., aged 28 years, married 3 years and gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 5th January, 1952.

Main Complaints. Marked irregularity of the menses with episodes of menorrhagia of up to 4-weeks duration, and commencing hirsutism.

Menarche at 14 years. The menses were irregular from the onset, occurring for 3 to 21 days every 2 weeks to 8 months.

General examination. Except for slight hirsutism of the face, trunk and extremities, nil abnormal was detected.

Pelvic examination. The only positive finding was some enlargement of the ovaries.

Operation. 10th January, 1952. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a somewhat thickened tunica, a large number of primordial follicles, a moderate number of developing and non-cystic follicles, and occasional cystic and atretic follicles. In some of the non-cystic follicles there are broad zones of actively growing granulosal, often luteinized, thecal and prothecal elements. All these zones have a high mitotic index. Most of the atretic follicles show very little activity. In only the occasional one is there some theca present. The cystic follicles show minimal amounts of both cell elements.

Conclusion. The pattern exhibited by these ovaries is that of an hyperthecosis ovarii in the late thecal-granulosal synergistic phase. It is most unfortunate that no endometrium was submitted with the ovaries.

Progress. Patient not traced.

GROUP 4. THE EARLY THECAL DOMINANT PHASE

Characteristic Ovarian Microscopical Patterns: The overall pattern of the ovaries at this phase is one of slight thecal dominance. Small islands of theca cells usually begin to appear in the stroma. The relative amounts of theca and granulosa per ovary are dependent upon the stage at which the change over from the synergistic to the thecal dominant phases occurred. If this occurred before the late synergistic phase was reached then the amount of theca per developing, non-cystic and atretic follicle is not very different from that found in the earlier thecal-granulosal synergistic phases; the granulosa is, however, in nearly every non-cystic follicle a few cell layers thinner than the theca of that follicle. If the case had reached the late synergistic phase, however, before passing into the thecal dominant phase, then a number of non-cystic follicles may still exhibit thick zones of granulosa and theca but again here the overall amount of theca, including the thecal islands, is still somewhat greater than that of the granulosa.

Characteristic Endometrial Microscopical Patterns: Just as with the ovarian patterns of this phase so also are the endometrial patterns dependent upon the stage at which the change over from the synergistic to the thecal dominant phases occurred. Thus the patterns will vary

from crowding of glands, pseudostratification and glandular intussusception through cystic tendencies to frank swiss-cheese hyperplasias. The only apparent difference between the endometrium of this phase and its corresponding synergistic phase pattern may be a slight decrease in mitotic activity. However, this is a difficult feature to assess unless moderately marked. The probable reason for the relatively minor differences in appearance between the endometria of this phase and their corresponding synergistic phase endometria, is that at this phase the degree of thecal dominance is not sufficient to cause any but slight depression of endometrial activity.

Main Symptoms: (i) *Hirsutism and Irregular Menses*

Case 8. B.116. E.R.R., aged 27 years, married, gravida-0, was first seen at the Sterility Clinic of the Johannesburg General Hospital on the 14th March, 1951.

Main Complaints. Sterility, deteriorating menstrual regularity, and increasing hirsutism.

Menarche at 13 years. The menses were always irregular, particularly latterly when they became 5 days/1–3 months.

General examination. Except for marked hirsutism of the face, trunk and extremities, and a male type of pubic escutcheon, nil abnormal was detected.

Pelvic examination. The only positive findings were a small uterus, and firm insensitive somewhat enlarged ovaries.

Operation. 29th March, 1951. A diagnostic curettage was done.

Microscopical findings of endometrium. The main features of this endometrium are their marked crowding together of glands and pseudostratification of gland cells; a pattern which, on superficial examination, simulates adenocarcinoma (Fig. 5). Some glands exhibit irregular tufting, a few contain glandular epithelium in their lumina, others show a cystic tendency and the odd gland is cystic but irregularly tufted. The stromal cells are in parts differentiated to a degree beyond that of the gland cells. Active mitosis is present in both the glands and stroma.

Conclusion. The marked crowding together of glands, pseudostratification of cells, glandular inclusions and cystic tendency of occasional glands are all suggestive of this being a case of hyperthecosis ovarii in the intermediate thecal-granulosal synergistic phase.

In view of the above findings an ovarian wedge resection was suggested to the patient. It was not until 6 months later, however, that consent was received for the operation.

Operation. 20th September, 1951. A bilateral ovarian wedge resection was done. Both ovaries were somewhat enlarged and exhibited thickened tunicae.

Microscopical findings of ovaries. Sections taken from a number of different areas of each ovary exhibit a thickened tunica, cellular stroma, a large number of primordial follicles, a number of cystic follicles and follicles undergoing atresia, a few atretic follicles, a number of small islands of theca cells scattered throughout the stroma (Fig. 11) and areas of prothecal development. Although the amount of thecal activity present in the atretic follicles and follicles undergoing atresia is not more than that found in ovaries of the earlier thecal-granulosal synergistic phases (Fig. 12), the amount of granulosa in the non-cystic follicles is usually a few cell layers thinner than the theca. The result is, taking into account the many islands of theca cells scattered throughout the stroma, commencing thecal dominance.

Conclusion. The patterns exhibited by these ovaries are those of a case of hyperthecosis ovarii in the early thecal dominant phase.

Progress. 22nd April, 1952. A biopsy curettage at this time revealed a secretory endometrium in the early stages of menstrual desquamation. The menses are now regular, occurring approximately every 28 days, the previous period having occurred on the 24th March, 1952. The temperature charts show evidence of ovulation and the hirsutism is improving.

3rd June, 1953. The patient is now a few weeks pregnant. This fact has been confirmed by a biological test.

Main Symptoms: (ii) *Hirsutism, Irregular Menses and Bouts of Amenorrhoea*

Case 9. B.460. J.K., aged 23 years, unmarried, was first seen by a gynaecologist in private practice in Johannesburg on the 1st June, 1952.

Main Complaints. Marked irregularity of the menses and increasing hirsutism. Both these complaints appeared to be aggravated by so-called X-ray stimulation of the ovaries and pituitary 1 year previously.

Menarche at 14 years; the menses being irregular from the onset occurring approximately every 3–6 months. Two years later, at the age of 16 years, hirsutism started developing.

General examination. Except for hirsutism of the face, trunk and extremities, nil abnormal was detected.

Pelvic examination. The only apparent pathology was enlargement of the ovaries.

Operation. 18th June, 1952. A bilateral ovarian wedge resection and diagnostic curettage was done.

Microscopical findings. (a) *Ovaries:* Sections of both ovaries exhibit a large number of primordial follicles, a few non-cystic follicles with normal amounts of both the thecal and granulosal elements, occasional cystic follicles and a number of atretic follicles. In some of these latter follicles the theca is undergoing fibrosis whilst in others it is present in either normal amounts or slightly in excess of the normal.

(b) *Endometrium:* Sections of the endometrium exhibit tubular glands with a pseudostratified cell pattern. Relatively few mitotic figures are seen.

Conclusion. The somewhat depressed endometrium and the patterns presented by the ovaries, with their slight thecal dominance, are suggestive of this being a

case of hyperthecosis ovarii in the early thecal dominant phase.

Progress. 24th March, 1953. The menses are now perfectly regular, the periodicity being 4–5/27–28 days. There is, however, no improvement of, or deterioration in, the hirsutism.

Case 10. G.4145. L.D., aged 25 years, married 2½ years, gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 6th October, 1951.

Main Complaints. Prolonged bouts of amenorrhoea, sterility and generalized hirsutism.

Menarche at 13 years. The menses were regular for only a few months and then became 4–5 days/3–6 weeks until about the age of 18 years when the patient developed bouts of amenorrhoea of up to 9 months duration.

General examination. Except for a generalized hirsutism nil abnormal was detected. The configuration was feminine.

Pelvic examination. The uterus was of normal size but both ovaries were somewhat enlarged, particularly the right.

Laboratory findings. The basal metabolic rate and blood sugar estimations were normal. The neutral 17-ketosteroid estimation yielded a result of 8 mg. per 24 hour specimen of urine.

Operation. 22nd October, 1951. A bilateral ovarian wedge resection and appendicectomy was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a thickened tunica, a few cystic follicles, a number of non-cystic follicles and follicles undergoing atresia, a few atretic follicles, moderately thick zones of protheca around a number of follicles and a few small islands of theca cells scattered throughout the stroma. The cystic follicles exhibit only slight thecal-granulosal activity. In the non-cystic follicles the amount of thecal-granulosal activity is within normal limits, the theca, if anything, being present in slightly greater amounts than the granulosa. The atretic follicles and follicles undergoing atresia are either becoming fibrotic or exhibit normal amounts of theca.

Conclusion. The pattern presented by these ovaries with their slight thecal dominance is that of a hyperthecosis ovarii in the early thecal dominant phase.

Progress. 3rd December, 1953. The menses are now perfectly regular, the periodicity being 5/31–32 days. There is, however, as yet no improvement of, or deterioration in, the hirsutism.

Case 11. B.313. E.T., aged 25 years, married, para-1, gravida-1, was first seen by a gynaecologist in private practice in Johannesburg on the 1st December, 1951.

Main Complaints. Excessive hirsutism since the age of 19 years and marked irregularity of the menses with episodes of amenorrhoea of up to 5-months duration.

Menarche at 14 years. The menses were irregular from the onset being associated with episodes of amenorrhoea. After many years of trying to fall pregnant the patient gave birth to her only child 2½ years ago. This child was breast-fed for only a few weeks. Soon after this event the menstrual irregularities and hirsutism became even worse than they were prior to the pregnancy.

General examination. Except for a very marked degree of hirsutism of the face, trunk and extremities, nil abnormal was detected.

Pelvic examination. The only positive findings were a uterus which was somewhat smaller than normal and markedly enlarged, firm, insensitive ovaries.

Laboratory findings. The neutral 17-ketosteroid estimation yielded a result of 12·7 mg. per 24-hour specimen of urine.

Operation. 3rd December, 1951. A diagnostic curettage and bilateral ovarian wedge resection was done.

Microscopical findings. (a) *Ovaries:* Sections of both ovaries exhibit a thickened tunica, a large number of primordial follicles, some cystic, non-cystic and atretic follicles, a few developing follicles and a number of theca cell islands scattered throughout the stroma. In the cystic follicles very little thecal or granulosal activity is seen. Although the amount of theca cells in the non-cystic and atretic follicles is not much more than normal, these cells together with the thecal islands are present in a somewhat greater amount than the granulosa cell.

(b) *Endometrium:* Sections of the endometrium exhibit round, tubular and irregularly tufted glands, the cells in some exhibiting pseudostratification. An interesting feature in this endometrium is the number of gland cells exhibiting infranuclear vacuolation in spite of the absence of corpora lutea in the ovaries. A fair number of mitotic figures are seen in the gland and stromal cells.

Conclusion. The patterns presented by these ovaries with their slight thecal dominance suggest that this is a case of hyperthecosis ovarii in the early thecal dominant phase.

Progress. 14th February, 1952. The 1st and 2nd menstrual periods, following the operation, occurred on the 27th December, 1951 and the 23rd January, 1952. This latter period was rather scanty and the patient was found to be pregnant. Associated with this event, as with the previous pregnancy, there was an aggravation of the hirsutism.

Case 12. B.353. E.P., aged 28 years, married, gravida-0, was first seen at the Johannesburg Hospital on the 16th February, 1952.

Main Complaint. Marked irregularity of the menses and commencing hirsutism.

Menarche at 15 years. The menses were reasonably regular for only the 1st year of their onset and then they became grossly abnormal, occurring approximately every 4–5 months.

General examination. Except for slight hirsutism of the face, trunk and extremities nil abnormal was detected.

Pelvic examination. The only positive finding was some enlargement of the ovaries.

Operation. 21st February, 1952. A diagnostic curettage was done.

Microscopical findings of endometrium. The endometrium shows a mixed gland pattern. The large majority of glands are tubular with lumina ±1 cell height in

diameter, occasional glands are irregularly shaped, a few are somewhat cystic and some contain glandular epithelium in their lumina. All the tubular glands exhibit fairly marked pseudostratification. The stroma is loose and oedematous. A fair number of mitotic figures occur in both the gland and stromal cells.

Conclusion. The appearance of this endometrium is suggestive of hyperthecosis ovarii.

In view of the above findings the patient was operated upon again on the 26th February, 1952.

Operation. 26th February, 1952. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a somewhat thickened, fibrous tunica, a number of primordial follicles, some early developing, non-cystic and cystic follicles and a number of regressing and atretic follicles. In the early developing and non-cystic follicles the thecal-granulosal ratios are within normal limits. In the cystic follicles the granulosal element is either absent or very attenuated whilst the theca is present in layers of not more than 3-cell layers in thickness. Thecal activity around the atretic follicles is perhaps slightly more than normal. Most of the follicles exhibit zones of protheca.

Conclusion. The appearance of these ovaries with their slight thecal dominance is that of an hyperthecosis ovarii in the early thecal dominant phase.

Progress: 25th September, 1953. A recent endometrial biopsy removed on the 25th day of the cycle shows some evidence of secretory activity. The menses have been occurring every month but the periodicity is still somewhat irregular. There has been very little improvement in the hirsutism even on cortisone therapy.

17th December, 1953. The patient is now approximately 8-weeks pregnant.

Case 13. C.51. I.F., aged 20 years, married and gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 28th March, 1953.

Main Complaints. Marked irregularity of the menses, sterility and commencing hirsutism.

Menarche at 14 years. The menses were irregular from the onset, there being bouts of amenorrhoea of up to 8 months.

General examination. Except for some hirsutism of the face, trunk and extremities, nil abnormal was detected. The configuration was feminine.

Pelvic examination. The only positive findings were a uterus somewhat smaller than normal and enlarged insensitive ovaries.

Laboratory findings. The total neutral 17-ketosteroid estimation was 14·4 mg. per 24 hour specimen of urine.

Operation. 2nd February, 1953. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit somewhat thickened tunicae, a moderate number of primordial follicles, some early developing follicles, only an occasional non-cystic follicle, some cystic follicles, a number of atretic follicles, and zones of prothecal activity around a number of the follicles. In the occasional non-cystic follicle the amount of granulosa and theca is within normal limits. In the cystic follicles these 2 elements are somewhat attenuated, the granulosal element being in parts no more than 3 cells in thickness and the theca perhaps only slightly more. In the atretic follicles the thecal activity is fair to moderate in amount. The stroma is somewhat cellular, but no thecal islands are seen.

Conclusion. The pattern presented by these ovaries with their relatively equal amounts of theca and granulosa around cystic and non-cystic follicles, and only fair to moderate amounts of thecal activity in atretic follicles, suggests that this is a case of hyperthecosis ovarii probably in the early thecal dominant phase.

Progress. 20th June, 1953. For the first time in her life the patient has now had 4 perfectly normal menstrual periods.

13th September, 1953. The patient is now approximately 2-months pregnant.

Main Symptoms: (iii) *Menorrhagia*

Case 14. B.533. B.P., aged 27 years, married, para-4 and gravida-5, was first seen at the Johannesburg General Hospital on the 2nd August, 1952.

Main Complaint. Marked menorrhagia since undergoing a Caesarean section operation in March, 1952.

Menarche at 12 years. The menses prior to the above operation were always regular being 5/30 days.

Obstetrical history. In May, 1950, whilst undergoing a curettage for retained products of conception, following the birth of her third child, the uterus was perforated and required suturing. Because of this a Caesarean section was done for the delivery of the fourth child on the 15th March, 1952, and at the same time the patient was sterilized. The child was breast fed for only 3 weeks.

On the 7th May, 1952, i.e., less than 2 months following the birth of this child the patient had a normal menstrual period. The period in June was excessive and after only a short interval bleeding recommenced. Because of its persistence the patient was admitted for a curettage.

General examination. Nil abnormal was detected, there being no evidence of hirsutism.

Pelvic examination. The only positive finding was slight enlargement of the ovaries.

Operation. 5th August, 1952. A diagnostic curettage was done.

Microscopical findings of endometrium. The endometrium shows a somewhat dissociated reaction between the stromal and gland cells in that the stromal cells in parts are moderately well defined whilst the gland cells are undifferentiated. In some areas the glands exhibit marked pseudostratification, whilst in other parts there is a frank swiss-cheese pattern (Fig. 10). Occasional glands exhibit glandular epithelium in their lumina. There is very active mitosis present both in the gland and stromal cells.

Conclusion. The appearance of this endometrium is suggestive of this being a case of hyperthecosis ovarii in the late thecal-granulosal synergistic phase. In spite of the curettage bleeding persisted and for this reason the

patient was operated upon again on the 18th September, 1952.

Operation. 18th September, 1952. A subtotal hysterectomy plus unilateral oöphorectomy and wedge resection of the opposite ovary was performed.

Microscopical findings. (a) *Ovaries:* Although in the large majority of follicles the granulosal element is rather attenuated and is present in layers of only 1 to 2 cells, in a few follicles it is luteinized and is present in either normal amounts or slightly in excess of the normal. The thecal element, on the other hand, is relatively prominent in atretic follicles and follicles undergoing atresia, there being in parts fairly thick zones of these cells (Fig. 13). Around a number of the latter follicles zones of protheca occur.

(b) *Endometrium:* Although this endometrium was removed only 6 weeks following the previous report it is somewhat attenuated. This may be due, in part, to the curettage. It is only 3 mm. thick and except for a few cystic glands which are still present the large majority of glands are tubular (Fig. 14). There is a fair degree of mitotic activity still present.

Conclusion. The patterns presented by the ovaries with their moderately thick zones of theca and luteinized granulosa, and the somewhat attenuated endometrium which still exhibits some somewhat cystic glands, are all suggestive of this case having now passed from the late thecal-granulosal synergistic phase into the early thecal dominant phase and perhaps it is even on the verge of passing into the intermediate dominant phase.

Group 5. The Intermediate Thecal Dominant Phase

Characteristic Ovarian Microscopical Patterns: The ovaries at this stage exhibit in addition to thickened tunicae, non-cystic, cystic and only early developing follicles, and often islands of theca cells scattered throughout the stroma, atretic follicles with zones of thecal activity which are in excess of the normal. The thickness of these zones, however, is not as marked as that found in the late dominant phase.

Characteristic Endometrial Microscopical Patterns: Although the endometrium at this stage exhibits a similar range of gland patterns to that found in the early thecal dominant phase, the decrease in mitotic activity is more marked.

Main Symptoms: (i) *Hirsutism, Severe Dysmenorrhoea and Irregular Menses*

Case 15. C.110. P.F., aged 27 years, married 2 years, gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 5th June, 1953.

Main Complaints. Marked dysmenorrhoea, sterility and menstrual irregularity.

Menarche at 14 years. The menses, which have always been accompanied by severe dysmenorrhoea, were fairly normal until approximately 4 years ago when they became somewhat irregular with a periodicity of 7–10 days/4–6 weeks.

General examination. Except for marked hairiness of the legs nil abnormal was detected.

Pelvic examination. The only positive findings were a fixed, retroverted uterus, and immobile tender adnexal masses. In view of these findings and the history of marked dyspareunia and dysmenorrhoea a tentative diagnosis of endometriosis was made and a laparotomy was, therefore, recommended to the patient.

Operation. 8th June, 1953. At laparotomy numerous adhesions were found in the pelvis and the ovaries, which were the site of a number of chocolate cysts, exhibited the typical appearances of hyperthecosis. A bilateral ovarian wedge resection was, therefore, done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a thickened tunica, a very occasional primordial and early developing follicle, a moderate number of cystic and non-cystic follicles, a moderately large number of atretic follicles, zones of prothecal activity, a mature corpus luteum and a number of typical islands of endometriosis (Fig. 15). Although the cystic follicles exhibit very little thecal-granulosal activity, the occasional non-cystic follicle shows a moderate amount of both these elements, the granulosa, in parts, being as much as 10 cells in thickness. In many of the atretic follicles the amount of thecal activity is more than that found in the early thecal dominant phase (Fig. 16). An interesting feature of the corpus luteum is the marked amount of para-lutein tissue (Fig. 17).

Conclusion. The pattern presented by the ovaries with their islands of endometriosis suggests that this is a case of hyperthecosis ovarii apparently passing into the intermediate thecal dominant phase.

Main Symptoms: (ii) *Hirsutism, Irregular Menses and Bouts of Amenorrhoea*

Case 16. C.76. J.H.H., aged 22 years, married 2 years, gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 10th February, 1953.

Main Complaints. Marked irregularity of the menses, increasing hirsutism and sterility.

Menarche at 15 years. The menses were irregular from the onset. Hirsutism first started developing 2 years ago and during this period bouts of amenorrhoea of up to 2–3 months have occurred.

General examination. Except for a generalized hirsutism nil abnormal was detected.

Pelvic examination. The only positive findings were a small uterus and moderately enlarged somewhat insensitive ovaries.

Operation. 13th February, 1953. A diagnostic curettage was done.

Microscopical findings of endometrium. The large majority of endometrial glands are tubular, an occasional one is cystic (Fig. 18) and a few exhibit glandular inclusions in their lumina. In parts the gland cells show evidence of pseudostratification. The stroma is on the

whole compact. Only an occasional mitotic figure is seen in either the gland or stromal cells.

Conclusion. The pattern presented by this endometrium with its paucity of mitotic figures is suggestive of this being a case of hyperthecosis ovarii in a thecal dominant phase.

In view of the above findings the patient was re-operated upon 2 months later on the 17th April, 1953.

Operation. 17th April, 1953. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a moderate number of primordial follicles, a large number of atretic follicles and follicles undergoing atresia, and a few cystic and non-cystic follicles. Although the latter type of follicle still exhibits in parts fairly thick areas of granulosa and theca, the amount of atretic follicles and follicles undergoing atresia, with their patchy areas of moderately thick zones of thecal activity (Figs. 19 and 20)—zones thicker than that found in the early thecal dominant phase—is such that there is a very definite thecal dominance in these ovaries. Zones of protheca, in parts rather thick, occur around many of the above follicles (Figs. 21 and 21a).

Conclusion. The pattern exhibited by these ovaries, is that of an hyperthecosis ovarii in the intermediate thecal dominant phase.

Progress. 29th June, 1953. For the first time in her life the patient has now had 2 perfectly normal menstrual periods.

Case 17. B.405. J.D., aged 24 years, married, para-0, gravida-3, was first seen by a gynaecologist in private practice in Johannesburg on the 25th April, 1953.

Main Complaints. Gross irregularity of the menses, and marked hirsutism requiring daily shaving.

Menarche. The menses were reasonably regular until the last miscarriage which occurred in 1951. Soon after this episode the patient started becoming hirsute and the periods grossly abnormal with bouts of amenorrhoea of up to 3–4 months. These features so depressed the patient that she attempted suicide on 3 occasions.

General examination. The clitoris was approximately twice the normal size. The uterus was smaller than normal and both ovaries rather enlarged.

Laboratory findings. The neutral 17-ketosteroid estimation was 7·7 mg. per 24 hour specimen of urine.

Operation. 29th April, 1952. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a moderately thickened tunica, a number of primordial follicles, some cystic follicles with very little granulosal or thecal activity, a few non-cystic follicles with normal amounts of both cellular elements, a number of atretic follicles with moderately thick areas of theca cells and a fair number of small thecal islands scattered throughout the stroma. In addition there is in the one ovary a mature corpus luteum in which the paraluteal element appears to be present in excess of the normal. Around a number of the non-cystic follicles thick zones of protheca occur.

Conclusion. The pattern exhibited by these ovaries with many of their atretic follicles exhibiting zones of thecal activity greater than that found in the early thecal dominant phase suggests that this is a case of hyperthecosis ovarii in the intermediate thecal dominant phase.

Progress. 9th June, 1952. The patient has now had 2 perfectly normal menstrual periods. The hirsutism as yet, however, shows no improvement. Further follow-up of this case has, unfortunately, not been possible.

Main Symptoms: (iii) *Hirsutism and Persistent Amenorrhoea*

Case 18. B.380. S.L., aged 23 years, single, gravida-0, was first seen at the Coronation Non-European Hospital on the 20th March, 1952.

Main Complaints. Persistent amenorrhoea for the last 11 months and increasing hirsutism of the face, trunk and extremities. During the 2 years prior to the former episode the patient had long bouts of menorrhagia.

Menarche at 13½ years. The menses were irregular from the onset with a periodicity of 5–7/30–90 days.

General examination. Except for a generalized hirsutism nil abnormal was detected.

Pelvic examination. Owing to the fact that the patient was a virgo intacta no pelvic examination was possible.

Laboratory findings. The 17-ketosteroid estimations done on 2 occasions prior to the operation were 9·9 mg. and 7·1 mg. per 24-hour specimen of urine. Radiography of the pituitary fossa showed no abnormality.

Operation. 1st April, 1952. A diagnostic curettage was done. The vaginal examination revealed a small uterus and enlarged ovaries, particularly the right.

Microscopical findings of endometrium. The endometrium exhibits a varied gland pattern. Many glands are small round and tubular; some contain glandular inclusions in their lumina; many show a cystic tendency (Fig. 22), and the occasional gland is grossly cystic (Fig. 23). Many of the former glands exhibit pseudostratification of their cells. Only a very occasional mitotic figure is seen.

Conclusion. The pattern exhibited by the endometrium with its paucity of mitotic figures and occasional cystic gland suggests that this case was once in either the intermediate or late thecal-granulosal synergistic phase and now, probably as a result of increasing thecal activity, has passed into a thecal dominant phase. In view of the above findings a laparotomy was performed on the 9th April, 1952.

Operation. 9th April, 1952. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a large number of primordial follicles, some early developing and non-cystic follicles, a few cystic follicles, a number of regressing and atretic follicles and scattered throughout the stroma small islands of theca cells (Fig. 24). Whereas in the developing and some of the non-cystic follicles normal amounts of granulosa and theca, both often luteinized, occur, in the cystic follicles these elements are atrophied. Many of the atretic follicles, on the other hand, exhibit in parts

moderately thick areas of markedly luteinized theca cells, which bear a close resemblance to those of the adrenal gland (Fig. 25). Very broad zones of prothecal activity occur around many follicles, particularly those undergoing atresia (Fig. 26).

Conclusion. The pattern exhibited by these ovaries with their preponderance of theca over granulosa cells, a preponderance greater than that found in the early thecal dominant phase, suggests that this is a case of hyperthecosis ovarii in the intermediate thecal dominant phase.

Progress. 20th August, 1952. The patient is now having perfectly regular menses occurring approximately every 28–32 days. There has been a slight improvement in the hirsutism. Unfortunately no further follow-up has been possible in this case.

Main Symptoms: (iv) *Hirsutism, and Irregular Menses with Bouts of Amenorrhoea and Menorrhagia*

Case 19. B.434. J.A.J.C., aged 36 years, married 8 years, gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 5th April, 1952.

Main Complaint. Marked irregularity of the menses and increasing hirsutism.

Menarche at 16 years. The menses were irregular from the onset, occurring for 2 to 3 days every 2 to 3 months. Following an episode of 2-months amenorrhoea in January and February, 1952 the patient began to bleed more or less continuously and was still bleeding when first seen in April, 1952.

General examination. There was marked hirsutism of the face and trunk, and especially of the extremities.

Pelvic examination. The only positive finding was some enlargement of the ovaries particularly the left.

Operation. 7th April, 1952. A bilateral ovarian wedge resection and uterine curettage was done.

Microscopical findings. (a) *Ovaries:* Sections of both ovaries show in addition to a preponderance of atretic and cystic follicles a number of developing and non-cystic follicles. Although the latter 2 types of follicles exhibit both granulosal and thecal activity, which in parts is somewhat thick, the amount of atretic follicles, with their patchy areas of moderately thick zones of thecal activity, is so predominant that there is a very definite thecal dominance in these ovaries. Zones of prothecal activity occur around many of the above follicles.

(b) *Endometrium:* The endometrium exhibits a varied glandular pattern. Most of the glands are tubular, some are slightly cystic and the occasional gland is definitely cystic. A feature common to all these glands is marked pseudostratification of their cells. Although on superficial examination the endometrium appears rather active only occasional mitotic figures are seen.

Conclusion. The patterns exhibited by the ovaries with a number of their follicles still exhibiting moderately thick areas of thecal-granulosal activity but with a predominance of atretic follicles showing thick zones of theca, and the endometrium with its occasional cystic glands but paucity of mitotic figures, all suggest that at one stage this case was in the intermediate thecal-granulosal synergistic phase but now, as a result of increasing thecal dominance—a degree of dominance greater than that found in the early thecal dominant phase—has passed into the intermediate thecal dominant phase.

Progress. June, 1952. The patient, for the first time in her life, has now had 3 perfectly normal menstrual periods. No change, however, has as yet occurred in the hirsutism.

Case 20. B.242. P.M., aged 31 years, married 7 years, gravida-0, was first seen at the Johannesburg General Hospital on the 21st August, 1951.

Main Complaints. Persistent vaginal bleeding for the last 6 weeks, at times excessive, and increasing hirsutism of the face, trunk and extremities.

Menarche. Following one vaginal bleeding at 11 years no further bleeding occurred until the age of 14 when regular, approximately 28-day, menstrual cycles were established. This menstrual rhythm continued until the age of 17 years when it became irregular with bouts of amenorrhoea of up to 3–4 months. Recently there have been long episodes of menorrhagia, the last, immediately prior to admission, having persisted for 6 weeks as already stated.

General examination. Except for slight generalized hirsutism nil abnormal was detected.

Pelvic examination. The only positive findings were a rather small infantile uterus and moderately enlarged ovaries.

Operation. 28th August, 1951. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a fair number of cystic, and a few non-cystic and atretic follicles. The thecal-granulosal elements in the cystic follicles are minimal in amount. In the non-cystic follicles the thecal zones are moderately broad and the granulosal element 4–5 cells in thickness. These latter follicles exhibit fairly thick areas of protheca as well. The atretic follicles show fair amounts of thecal activity. The stroma is rather cellular and scattered throughout it are a large number of thecal islands, many of them exhibiting as many as 20–40 cells.

Conclusion. The relatively small amount of granulosa cells, as compared with the fair amounts of thecal activity in the atretic follicles, and the large number of theca cell islands scattered throughout the stroma, are all suggestive of this being a case of hyperthecosis ovarii in the intermediate thecal dominant phase.

Progress. 11th August, 1952. The patient now feels very well and energetic. Her menses are absolutely regular being 5/30 days. There is as yet, however, no pregnancy or improvement in the hirsutism.

Group 6. The Late Thecal Dominant Phase. (Type 1)

Characteristic Ovarian Microscopical Patterns: In addition to the features already described for

the intermediate thecal dominant phase many of the atretic follicles at this stage exhibit marked thecal activity and the islands of theca cells found in the stroma are often large.

Characteristic Endometrial Microscopical Patterns: The endometrium at this phase, although still exhibiting a similar range of gland patterns to that described for the early thecal dominant phase, is all but completely depressed as exemplified by the occurrence of only the very occasional mitotic figure.

Main Symptoms: (i) *Hirsutism, and Irregular Menses with Bouts of Amenorrhoea and Menorrhagia*

Case 21. B.383. A.W.C., aged 29 years, married 1943, divorced 1951, para-0, gravida-1, was first seen at the Johannesburg General Hospital on the 29th March, 1952.

Main Complaints. Marked irregularity of the menses with long bouts of amenorrhoea and episodes of menorrhagia, commencing hirsutism of the face, trunk and extremities and loss of libido.

Menarche at 13 years. The menses were irregular from the onset, occurring for 18–27 days every 4–6 months.

Obstetrical history. Although the patient was very keen on having a child from the commencement of her marriage she remained sterile for 7 years and then fell pregnant only to have a 3-months miscarriage in October, 1950.

General examination. Except for some hirsutism of the face, trunk and extremities, nil abnormal was detected.

Pelvic examination. The uterus was somewhat smaller than normal measuring 2½ inches with a uterine sound. Both ovaries were very enlarged and prolapsed.

Laboratory findings. The 17-ketosteroid estimation was 3·9 mg. per 24-hour specimen of urine. The fasting blood sugar was 87 mg.

In view of the abnormal menstrual history a diagnostic curettage was done on the 3rd April, 1952.

Microscopical findings of endometrium. The endometrium shows a varied glandular pattern. The large majority of glands are small round and tubular, many of them exhibiting a moderate degree of pseudostratification; some show a cystic tendency, a few are grossly cystic and quite a number of glands exhibit glandular epithelium in their lumina (Fig. 27). The stroma is compact and on the whole poorly differentiated. Only a very occasional mitotic figure is seen in either the gland or stromal cells.

Conclusion. The microscopical pattern exhibited by the endometrium suggests that this was a case of cystic glandular hyperplasia which now is becoming depressed, probably as a result of increasing thecal activity in the ovaries.

In view of these endometrial findings the patient was operated upon again on the 15th April, 1952, i.e., approximately 2 weeks following the curettage.

Operation. 15th April, 1952. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit very occasional early developing follicles, a large number of cystic and non-cystic follicles, a smaller number of atretic follicles, many of them exhibiting zones of protheca, and scattered throughout the stroma small islands of theca cells. In the cystic follicles the amount of granulosa and theca is very slight. In the non-cystic follicles, although many of them still contain some granulosa, the thecal element is very much more prominent. In the atretic follicles there are in parts very thick zones of thecal activity (Fig. 28).

Conclusion. The patterns presented by the endometrium with its paucity of mitotic figures and the ovaries with many of their atretic follicles exhibiting marked thecal activity suggest that this is a case of hyperthecosis ovarii in the late thecal dominant phase (Type 1).

Progress. 13th August, 1952. The patient for the first time in her life is now having regular menses, but the amount of bleeding is somewhat excessive lasting as it does for about a week. She feels very well and there is an improvement in the libido. There is, however, very little change in the hirsutism.

Main Symptoms: (ii) *Slight Hirsutism and Irregular Menses with Bouts of Amenorrhoea*

Case 22. G.7088. I.P., aged 27 years, married, para-1, gravida-1, was first seen by a gynaecologist in private practice in Johannesburg on the 16th April, 1953.

Main Complaints. Marked irregularity of the menses and sterility.

Menarche at 13 years. The menses were reasonably regular until the age of 16 years when they became very abnormal with a periodicity of 7 days/2–6 months. After trying to become pregnant for a number of years the patient gave birth to a full-time infant in December, 1951. This child was breast-fed for 9 months. During the 6th month post-partum, in June, 1952, the patient had her first menstrual period since falling pregnant. Two more menstrual periods followed in December, 1952 and January, 1953, and then the patient became amenorrhoeic.

General examination. The only hirsutism present was on the abdomen. The blood pressure was 118/80. Neither albuminuria nor glycosuria were observed.

Pelvic examination. The uterus was retroverted, and smaller than normal. The ovaries were enlarged particularly the right.

Operation. 29th April, 1953. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a moderately thickened tunica, a moderate number of primordial follicles, a large number of atretic follicles, some cystic follicles, a few non-cystic follicles, and an occasional early developing follicle. The atretic follicles exhibit, in parts, very thick zones of theca and protheca. The cystic follicles, on the other hand, show very little if any of either of the cellular elements. Only

in a few non-cystic follicles is there still some evidence of granulosal activity; this granulosa in the odd follicle is moderate in amount. The stroma is rather cellular and in parts very oedematous.

Conclusion. The large number of atretic follicles, many of them exhibiting very thick zones of thecal activity, suggest that this is a case of hyperthecosis ovarii in the late thecal dominant phase probably (Type 1), notwithstanding the fact that there are still present some follicles which exhibit a moderate amount of granulosal activity.

Progress. Unfortunately the patient has left Johannesburg and her new address is unknown.

Main Symptoms: (iii) *Hirsutism and Irregular Menses with Bouts of Amenorrhoea*

Case 23. G.7220. M.Z., aged 24 years, married 7 years, para-1, gravida-1, was first seen by a gynaecologist in private practice in Johannesburg on the 18th April, 1953.

Main Complaints. Marked irregularity of the menses, increasing hirsutism and sterility.

Menarche at 14 years. The menses were reasonably regular until the age of 17 years when they became grossly abnormal with a periodicity of 6–10 days/2–5 months.

Obstetrical history. The patient was married at the age of 17 years and although birth control methods were not adopted she failed to fall pregnant for more than 3 years. At the age of 21 she gave birth to her only child whom she breast fed for 4 months. Since then although she has been trying to fall pregnant again it has been without avail.

General examination. The patient was grossly hirsute over her entire body and exhibited typical acne scars and boils on her face and back. The blood pressure was 120/80. Neither albuminuria nor glycosuria was observed.

Pelvic examination. The uterus was small, anteverted and mobile and the right ovary somewhat enlarged. The left gonad was not palpated.

Operation. 18th May, 1953. A bilateral ovarian wedge resection and appendicectomy was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a thick fibrous tunica, a few primordial follicles, a moderate number of cystic and atretic follicles and follicles undergoing atresia, a few non-cystic follicles, an occasional early developing follicle, and, scattered throughout the stroma, some small islands of theca cells. In the very cystic follicles the amount of granulosa and theca is almost nil. In the non-cystic follicles, on the other hand, there are moderately broad areas of thecal-granulosal activity; in parts the granulosal zone being as much as 10–15 cells in depth. Many of the atretic follicles exhibit areas of marked thecal activity each of approximately 50 to 100 cells thick. The stroma is very loose and oedematous and in parts rather cellular. Almost every follicle, no matter its size, exhibits some prothecal activity.

Conclusion. It is unfortunate that the patient was not curetted at the time of operation since the endometrium may have assisted with the classification of this case. However, the fact that there are still present a number of non-cystic follicles with moderately thick areas of theca and granulosa, notwithstanding the marked thecal activity around a number of atretic follicles, suggests that this case is still a Type 1 late thecal dominant phase.

Progress. 25th June, 1953. The patient had her first normal menstrual period on the 18th June, 1953; 4½ weeks following the operation.

Case 24. B.549. J. du P., aged 22 years, single, was first seen at the Johannesburg General Hospital on the 21st August, 1952.

Main Complaints. Marked irregularity of the menses with long periods of amenorrhoea and increasing hirsutism.

Menarche at 16 years. The menses were irregular from the onset. At the age of 18 years the patient started becoming hirsute and this has become progressively worse. There have been no voice changes.

General examination. Except for generalized hirsutism, nil abnormal was detected.

Pelvic examination. The only positive finding was enlargement of the ovaries.

Operation. 22nd September, 1952. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit, in addition to a corpus luteum in one of them and an early dermoid cyst in the other, a thickened tunica, areas of protheca, a few developing and cystic follicles, a large number of atretic follicles and scattered throughout the stroma small islands of theca cells. In the cystic follicles the theca and granulosa cells are either atrophied or present in moderate amounts. In the atretic follicles, except for a few which exhibit rather marked thecal activity, the large majority show moderate amounts of theca cells.

Conclusion. The appearance of these ovaries with some of their atretic follicles showing marked thecal activity suggests that this is a case of hyperthecosis ovarii in the late thecal dominant phase probably Type 1.

Progress. 27th December, 1952. The patient now feels very much more energetic. For the first time in her life her menses are perfectly regular with a periodicity of 4–5/30 days. The hirsutism, however, shows as yet no improvement.

Case 25. C.136. C.A.S., aged 21 years, single, gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 8th July, 1953.

Main Complaints. Marked irregularity of the menses and excessive hirsutism.

Menarche at 13 years. The menses were markedly irregular from the onset with bouts of amenorrhoea of up to 8 months. Hirsutism started developing soon after the commencement of menstruation and has become progressively worse.

General examination. Except for marked hirsutism of the face, trunk and extremities nil abnormal was detected. The pubic escutcheon was masculine in type.

Pelvic examination. The only positive findings were a small anteverted uterus, and enlarged clitoris and ovaries.

Laboratory findings. The neutral 17-ketosteroid estimation was 12·2 mg. per 24-hour specimen of urine.

Operation. 14th July, 1953. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a thick fibrous tunica, a large number of primordial follicles, only an occasional very early developing follicle, a number of cystic follicles, a few non-cystic follicles, a large number of atretic follicles and follicles undergoing atresia, and scattered throughout the stroma many islands of theca cells. In the cystic follicles both the granulosa and theca are present in small amounts. Only in the occasional non-cystic follicle are there still patchy areas of moderately thick zones of granulosa cells. Although the large majority of atretic follicles exhibit only moderately broad areas of theca cells a few of these follicles show marked thecal activity. Zones of protheca occur around a number of the above follicles. An interesting feature in these ovaries is the occurrence of areas of hyalinization not unlike that found in theca cell tumours.

Conclusion. The clinical history and the pattern presented by the ovaries, with a number of their atretic follicles exhibiting marked thecal activity, suggest that this is a case of hyperthecosis ovarii in the late thecal dominant phase. Unfortunately, in view of the absence of endometrium, it is impossible to be sure as to what type this case belongs in and it has, therefore, been arbitrarily classified as a Type 1.

Case 26. B.126. M.M.M., aged 38 years, married, para-3, gravida-3 was first seen at the Johannesburg General Hospital on the 10th March, 1951.

Main Complaints. Marked irregularity of the menses, complete loss of libido, deepening of voice timbre and increasing hirsutism necessitating daily shaving.

Menarche at 12 years. The menses were perfectly regular until the birth of the patient's last child 12 years ago. Recently there have been bouts of amenorrhoea of anything up to 5 months.

Obstetrical history. The patient has had 3 children, their respective ages being 18, 14 and 12 years. All were put to the breast but the supply of milk was inadequate particularly during the last pregnancy. Within a month of the birth of this child the patient ceased lactating.

General examination. The patient was well built and somewhat obese. Her arms and legs were rather muscular. The abdomen was pendulous and there was marked obesity of the buttocks and thighs. There was a recession of the temporal hair line and marked hirsutism of the face, axillae, trunk and extremities. The pubic escutcheon was masculine in type. Acne was present on the back. The blood pressure was 116/80.

Pelvic examination. The only positive findings were a slightly enlarged clitoris, an anteverted mobile small uterus and markedly enlarged ovaries.

Laboratory and X-ray findings. The neutral 17-ketosteroid estimation was 15·6 mg. per 24-hour specimen of urine. The B.M.R. was +25. No abnormalities were revealed, on X-ray of the skull and intravenous pyelography, of either the pituitary fossa or adrenal glands respectively.

Operation. 15th March, 1951. A total hysterectomy plus bilateral salpingo-oöphorectomy was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit a thickened tunica, a moderate number of primordial follicles, an occasional early developing follicle, a large number of cystic and atretic follicles and follicles undergoing atresia, and some islands of theca cells scattered throughout the stroma. Some of the cystic follicles still exhibit fair amounts of both granulosa and theca. In a few of the follicles undergoing atresia there are still in patchy areas broad zones of granulosa. All the atretic follicles exhibit thecal activity, which in some is very thick. Around a number of follicles are broad areas of protheca. The ovarian stroma is rather cellular in parts.

Microscopical findings of endometrium. Sections of the endometrium show a variety of gland patterns. The large majority, which are tubular, exhibit marked pseudo-stratification. A few are irregularly tufted and some are somewhat cystic. The stroma is rather compact. Although on superficial examination the endometrium appears active the mitotic index is rather low.

Conclusion. The pattern exhibited by the ovaries and endometrium is that of a hyperthecosis ovarii. The fact that a number of atretic follicles exhibit very thick areas of thecal activity, and the endometrium some cystic glands but a paucity of mitotic figures, suggests that this case was at one time in the late thecal-granulosal synergistic phase but now as a result of marked thecal dominance has passed into the late thecal dominant phase (Type 1).

Progress. 18th September, 1952. The patient feels very well, her libido has returned to normal and she now has to shave only once every 2–3 weeks.

Main Symptoms: (iv) *Hirsutism and Irregular Menses with Bouts of Menorrhagia*

Case 27. B.441. S. van R., aged 22 years, married, nullipara, was first seen at the Johannesburg General Hospital on the 23rd May, 1952.

Main Complaints. Irregularity of the menses with episodes of excessive bleeding, and hirsutism of the face, trunk and extremities.

Menarche at 13 years. The menses were reasonably regular with a periodicity of 5/28 days until October, 1951, when the patient contracted rheumatic fever. Soon after this episode the menses became irregular.

General examination. Except for hirsutism of the face, trunk and extremities, nil abnormal was detected.

Pelvic examination. The only positive findings were a small uterus and somewhat enlarged ovaries.

Laboratory findings. The neutral 17-ketosteroid estimation was 6·3 mg. per 24-hour specimen of urine.

Operation. 26th May, 1952. At laparotomy the left ovary was found to be the site of a cyst 1½ inches × 1 inch × 1 inch. This cyst was removed and a bilateral ovarian wedge resection done.

Microscopical findings of ovaries. Sections of both

ovaries exhibit a thickened tunica, a large number of primordial follicles, a number of cystic and atretic follicles and follicles undergoing atresia, some non-cystic follicles, and in one of them an early corpus luteum with haemorrhage into its lumen. The granulosa and theca cells are atrophic in the cystic follicles. In the non-cystic follicles the amount of granulosa and theca is within normal limits. Some of the atretic follicles exhibit very thick zones of thecal activity, some of them being more than 100 cells in depth.

Conclusion. Unfortunately no endometrium was submitted with the specimen but the history of marked menorrhagia and the pattern presented by the ovaries, with some of their atretic follicles exhibiting marked thecal activity, suggests that this is a case of hyperthecosis ovarii in the late thecal dominant phase probably Type 1.

Progress. It has unfortunately been impossible to trace the patient since the operation.

Main Symptoms: (v) *Hirsutism and Irregular Menses with Bouts of Amenorrhoea and Menorrhagia*

Case 28. B.343. H.P., aged 20 years, married, para-1, gravida-1, was first seen by a gynaecologist in private practice in Johannesburg on the 10th February, 1952.

Main Complaints. Marked irregularity of the menses and commencing hirsutism of the face, trunk and extremities.

Menarche at 15 years. The menses were irregular from the onset with bouts of amenorrhoea, of up to 3-months duration, and episodes of menorrhagia.

Obstetrical history. The patient was married at the age of 16 years and fell pregnant soon afterwards, i.e., approximately 1 year following the onset of her menses. The child was born in December, 1948 and was breast fed for 18 months. During the ninth post-partum month menstruation recurred. The first 2 menstrual periods were more or less normal but then they became markedly irregular again. In spite of the fact that birth control was not practised following the birth of this child no further pregnancies resulted. At the age of 18 years hirsutism first started developing.

General examination. Except for slight hirsutism of the face, trunk and extremities nil abnormal was detected.

Pelvic examination. The uterus was retroverted and somewhat smaller than normal. Both ovaries were enlarged and firm.

Operation. 13th February, 1952. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit numerous follicles. Some are in the earlier stages of development, others are cystic, some are non-cystic and the majority are either undergoing atresia or are atretic. Most of these latter follicles exhibit broad zones of protheca. The developing and non-cystic follicles show normal amounts of both granulosa and theca, the former cells being luteinized in some of the follicles. In the cystic follicles the granulosal element is either attenuated or completely absent, but the thecal element is moderately thick in patches. In many of the atretic follicles broad zones of thecal activity are seen.

Conclusion. Unfortunately no endometrium was submitted with the specimen. However, the pattern exhibited by the ovaries suggests that this is a case of hyperthecosis ovarii in the late thecal dominant phase probably Type 1.

Progress. 15th April, 1952. The patient has now had 2 perfectly normal menstrual periods and the hirsutism shows marked improvement, nearly all the hair on the arms, legs and face having disappeared.

1st May, 1953. Five months following the above operation the patient fell pregnant and gave birth to a normal child on the 25th April, 1953.

Main Symptoms: (vi) *Hirsutism and Irregular Scanty Menses*

Case 29. B.424. E.J., aged 28 years, married, para-2, gravida-4 was first seen by a gynaecologist in private practice in Johannesburg on the 29th December, 1951.

Main Complaints. Scanty menses and increasing hirsutism.

Menarche at 13 years. The menses were irregular from the onset occurring for 2–3 days every 1 to 2 months. Since 1948, following an abortion, they have become very scanty.

General examination. Except for marked hirsutism of the legs and abdomen, and to a lesser degree of the face, nil abnormal was detected.

Pelvic examination. The only positive findings were a retroverted uterus, apparently of normal size, and very enlarged insensitive ovaries.

Laboratory findings. The neutral 17-ketosteroid estimation was 11·9 mg. per 24-hour specimen of urine.

Operation. 3rd January, 1952. A diagnostic curettage was done.

Microscopical findings of endometrium. Sections of the endometrium show a cystic glandular pattern with, in parts, marked crowding of glands. Many of the glands are cystically dilated and others contain glandular epithelium in their lumina. A moderate number of mitotic figures are seen in the gland and stromal cells.

Conclusion. The abnormal menstrual history, the marked hirsutism, and the cystic glandular pattern exhibited by the endometrium, are all suggestive of this being a case of hyperthecosis ovarii.

In view of the above findings a bilateral ovarian wedge resection was recommended to the patient, but her consent for the operation was only obtained in May, 1952, 5 months later, probably because of an aggravation of symptoms.

Operation. 15th May, 1952. At laparotomy both ovaries were much enlarged and sclerocystic. A bilateral ovarian wedge resection was done.

Microscopical findings of ovaries. Sections of both ovaries exhibit thickened tunicae, a number of cystic, non-cystic and atretic follicles, small islands of theca cells scattered throughout the stroma, and a mature corpus luteum in one of them. In the cystic follicles the granulosa is either absent or atrophied and the theca is present in only small amounts. In the large majority of

non-cystic follicles the amount of granulosa and theca is within normal limits. The most marked effect is seen in many of the atretic follicles where the theca is very thick and active. The amount of paralutein tissue in the corpus luteum appears to be in excess of the normal.

Conclusion. The appearance of these ovaries with many of their atretic follicles exhibiting very thick zones of thecal activity suggests that this is a case of hyperthecosis ovarii in the late thecal dominant phase. ? Type 1.

Progress. 8th September, 1952. The menses are now perfectly regular the periodicity being 7/30 days. The hirsutism shows improvement on the extremities and trunk and has almost completely disappeared from the face.

Group 6. The Late Thecal Dominant Phase. (Type 2)

Characteristic Ovarian Microscopical Patterns: The ovarian pattern at this stage is similar to that found in the late thecal dominant phase (Type 1) except for Case No. 30 (B.400) where, although the amount of theca in the follicles is relatively slight, the amount of granulosa is almost nil and thus is incapable of counteracting the thecal effect.

Characteristic Endometrial Microscopical Patterns: The endometrium is completely atrophic.

Main Symptoms: (i) *Irregular Menses with Bouts of Amenorrhoea and Episodes of Menorrhagia*

Case 30. B.400. A.K.B., aged 53 years, married, para-1, gravida-1, was first seen at the Johannesburg General Hospital on the 19th April, 1952.

Main Complaint. More or less continuous vaginal bleeding from March to April, 1952. This episode of bleeding was preceded by a period of 6-months amenorrhoea from July to December, 1951 and then 2 short episodes of bleeding in January and February, 1952.

Menarche at 17 years. The menses were always regular being 3/28 days until the episodes above described.

General examination. Except for slight stoutness, nil abnormal was detected. There was no evidence of hirsutism.

Pelvic examination. The uterus was anteverted and appeared to be of normal size. In the right adnexal region an ovarian cyst was felt.

Operation. 22nd April, 1952. In view of the above abnormal menstrual history a diagnostic curettage was done on the 22nd April, 1952.

Microscopical findings of endometrium. The endometrium exhibits a proliferative pattern. Except for a few very cystic glands (Fig. 6) and some that show a cystic tendency the large majority of glands are tubular (Fig. 7). A few are very irregularly shaped and some contain glandular epithelium in their lumina. A feature common to all these glands, no matter their shape, is the presence of fairly marked pseudostratification. Fairly active mitosis is present in both the gland and stromal cells.

Conclusion. The pattern exhibited by this endometrium with its fairly marked pseudostratification of gland cells and occasional cystic glands suggests that this is a case of hyperthecosis ovarii in the intermediate thecal-granulosal synergistic phase.

In view of the above findings and the patient's age a hysterectomy was recommended. However, consent for the operation was obtained only 2 months later on the 27th June, 1952 when a total hysterectomy plus bilateral salpingo-oöphorectomy was performed.

Microscopical findings. (a) *Ovaries:* Sections of both ovaries exhibit a thickened tunica, some cystic and atretic follicles and follicles undergoing atresia, and scattered throughout the stroma small islands of theca cells of 3–5 cells each. The cystic and atretic follicles exhibit no granulosal activity but zones of theca which, except for the odd somewhat thickened area, are only 4–6 cell layers thick (Fig. 29).

(b) *Endometrium:* There is a dramatic change in the appearance of this endometrium as compared with that of 2 months previously in that now it is completely atrophic (Fig. 30). All the glands are tending to run parallel to the surface, the stroma is compact, and no mitotic figures are seen in either the gland or stromal cells.

Conclusion. The atrophic endometrium and the pattern exhibited by the ovaries with their small amount of theca cells but almost complete absence of granulosal elements, makes this a case of hyperthecosis ovarii in the late thecal dominant phase (Type 2), notwithstanding the relative paucity of theca cells.

The only possible explanation for this dramatic change, in so short a period of time, is that 2 months previously the cystic follicles were probably non-cystic and thus exhibited both granulosal and thecal activity, but now, as a result of cystic degeneration of these follicles and a failure to develop new follicles, because of age, the granulosal element has been almost completely obliterated leaving thereby a predominance of theca cells.

Main Symptoms: (ii) *Hirsutism and Irregular Menses with Long Bouts of Amenorrhoea*

Case 31. G.4248. B.Y., aged 25 years, married, gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 20th October, 1951.

Main Complaints. Marked irregularity of the menses, amenorrhoea for the last 7 months, sterility and increasing hirsutism and weight.

Menarche at 11 years. The periods were perfectly regular being 7/28 days until the age of 20 when the patient began putting on weight, more than 20 pounds, and the menses started becoming irregular. This menstrual irregularity was associated with increasing episodes of amenorrhoea, some lasting for as long as 9 months. Two years later, at the age of 22 years, hirsutism started developing.

General examination. The patient was overweight and

there was a generalized hirsutism of the face, trunk and extremities, the pubic escutcheon being of the male type. The blood pressure was 110/70. Unfortunately the patient was not investigated from the metabolic aspect.

Pelvic examination. The uterus was small and anteverted. Both ovaries were enlarged and somewhat insensitive to pressure, particularly the left.

Operation. 5th November, 1951. A diagnostic curettage and bilateral ovarian wedge resection was done. The curettage yielded absolutely no endometrium.

Microscopical findings of ovaries. Sections of both ovaries exhibit a thickened tunica, a large number of atretic follicles and follicles undergoing atresia, some cystic follicles and only a very occasional non-cystic and early developing follicle. The atretic follicles exhibit on the whole marked theca cell hyperplasia, the pattern in parts simulating adrenal cells. Surrounding most of these latter follicles are broad zones of protheca exhibiting marked mitotic activity. The cystic follicles show only slight granulosal activity but moderately thick areas of theca. Only in the very occasional non-cystic follicle is there still some granulosal activity.

Conclusion. The complete absence of endometrium on curettage and the marked thecal activity in the ovaries classify this case as a hyperthecosis ovarii in the late thecal dominant phase (Type 2).

Progress. 10th April, 1952. The menses are now perfectly regular with a periodicity of 4/27–28 days. There has also been an improvement in the weight, the patient, up to date, having lost 12 pounds.

Main Symptoms: (iii) *Hirsutism and Complete Amenorrhoea*

Case 32. B.216. B.G., aged 24 years, unmarried, gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 18th July, 1951.

Main Complaints. Complete amenorrhoea for the last 4¼ years, excessive hirsutism requiring daily shaving and complete lack of libido. These features so depressed the patient that on 3 occasions she attempted suicide.

Menarche at 13 years. The menses were moderately regular for only the first 2 years of menstruation when they became abnormal and finally ceased at the age of 19 years. The hirsutism started developing soon after the onset of the irregular menses.

General examination. The patient was somewhat stout and markedly hirsute.

Pelvic examination. The only positive findings were a small anteverted uterus and markedly enlarged ovaries.

Laboratory findings. The 17-ketosteroid estimation was 6·4 mg. per 24-hour specimen of urine.

Operation. 21st July, 1951. A dilatation and curettage and bilateral ovarian wedge resection was done. The curettage yielded no endometrium.

Microscopical findings of ovaries. Sections of both ovaries exhibit a number of primordial and atretic follicles and follicles undergoing atresia, some cystic follicles, a very occasional early developing follicle and numerous thecal islands, of approximately 10–30 cells each, scattered throughout the stroma. Many of the atretic follicles and those undergoing atresia exhibit thick zones of thecal and prothecal activity. The cystic follicles show very little activity of either the thecal or granulosal elements.

Conclusion. The complete atrophy of the endometrium and the marked thecal dominance of the ovaries classify this case as a hyperthecosis ovarii in the late thecal dominant phase (Type 2).

Progress. 18th August, 1952. The menses are now regular occurring with a periodicity of 2–3/27–28 days and the libido is perfectly normal. The degree of hirsutism has so improved that the patient no longer requires to shave. Very little hair is now visible on the chest, abdomen and extremities. The patient's mental outlook is now normal; her fits of moodiness and depression having disappeared. An endometrial biopsy removed on the 24th August, 1952, shows a perfectly normal secretory pattern.

13th April, 1953. The patient reported that she had put on more than 10 pounds in weight and that her menses had become progressively more scanty until recently when it had lasted only 1 day. She was, therefore, referred to an endocrinologist who diagnosed her as a case of hypothyroidism and put her on thyroid therapy.

23rd June, 1953. The patient has lost 20 pounds on treatment and her last 2 menstrual periods have been perfectly normal again.

Case 33. B.297. J.C., aged 28 years, married, para-0, gravida-1, was first seen at the Johannesburg General Hospital, on the 1st November, 1951.

Main Complaints. Marked hirsutism, complete lack of libido, sterility and persistent amenorrhoea since discontinuing with oestrogenic therapy 11 months ago. The last natural menstrual period occurred in 1947.

Menarche at 12 years. The menses which were irregular from the onset, occurring for approximately 5 days every 1–2 months, became progressively worse until 1947 when they ceased entirely. Thyroid therapy and so-called X-ray stimulation of the ovaries proved of no avail. Oestrogenic therapy, although causing withdrawal bleeding, also proved of no permanent benefit.

General examination. The patient's configuration was masculine in type. The face, trunk and extremities were markedly hirsute and there was a temporal recession and patchy baldness of the hair on the head. No apparent voice changes were observed.

Pelvic examination. The only positive findings were a small uterus measuring 2 inches with the uterine sound, and markedly enlarged ovaries, particularly the right.

Operation. 6th November, 1951. A dilatation and curettage and bilateral ovarian wedge resection was performed. The curettage yielded absolutely no endometrium.

Microscopical findings of ovaries. Sections of both ovaries exhibit a large number of thecal islands (Fig. 31), atretic follicles and follicles undergoing atresia, some cystic follicles, a very occasional early developing follicle and a mature corpus luteum in one of them. The atretic follicles and those undergoing atresia exhibit very marked thecal activity (Fig. 32). Even the cystic follicles which contain very little granulosa show broad zones of

theca cells. An interesting feature in both ovaries is the development of areas of hyalinization in relationship to the thecal zones (Fig. 33); areas which are identical in appearance to those usually found in theca cell tumours.

Conclusion. The complete atrophy of the endometrium and the excessive thecal response of the ovaries classify this case as a hyperthecosis ovarii in the late thecal dominant phase (Type 2). The corpus luteum is probably the result of a freak ovulation.

Progress. 21st February, 1952. The patient's libido is now normal and her menses perfectly regular with a periodicity of 4–5/28–30 days. The uterus now measures 3 inches with the uterine sound and an endometrial biopsy removed on the 26th day of the cycle shows a perfectly normal secretory pattern (Fig. 34). There is, however, only slight improvement in the hirsutism, and the hair on the head, although it has ceased falling out, shows as yet very little melioration.

16th April, 1953. The patient is still having perfectly regular menses and is now trying to fall pregnant. The hair on the head is perhaps a little thicker than before but as yet shows no marked improvement.

Case 34. G.1308. E.K., aged 22 years, unmarried, gravida-0, was first seen by a gynaecologist in private practice in Johannesburg on the 20th May, 1949.

Main Complaints. Marked hirsutism and complete amenorrhoea for the past year.

Menarche at 13 years. The menses which were irregular from the onset occurred for approximately 3 days every 3 months until the age of 18 when there occurred an episode of 9-months amenorrhoea. This amenorrhoea was treated with hormones and so-called X-ray stimulation of the pituitary. It resulted in more or less regular menses for about a year but then the menstrual regularity again deteriorated and at the age of 21 the patient became completely amenorrhoeic. The hirsutism first started developing about 2 years following the onset of menstruation and has become progressively worse.

General examination. There was no evidence of adiposity. The blood pressure was 140/80 and there was a very marked degree of hirsutism over the whole body.

Pelvic examination. The only positive findings were a small atrophic cervix and uterus, and enlargement of both ovaries, particularly the right.

Laboratory findings. The neutral 17-ketosteroid estimation was 2·3 mg. per 24-hour specimen of urine. The basal metabolic rate was +18 per cent and there was no evidence of glycosuria.

Operation. 18th July, 1949. A bilateral ovarian wedge resection was done. The ovaries were hard and appeared fibrous on cutting.

Microscopical findings of ovaries. Both ovaries exhibit markedly thickened fibrous tunicae, several primordial follicles, a number of large corpora albicantia, only one atretic follicle and scattered throughout the stroma a moderate number of theca cell islands. These islands vary in size from approximately 10 to 60 cells and in many the cells are hyperplastic and are undergoing luteinization.

Conclusion. The pattern exhibited by the ovaries, with their islands of theca cells scattered throughout the stroma and complete lack of developing follicles suggest that this is a case of hyperthecosis ovarii which is passing from the late thecal dominant phase Type 2 into Type 3.

Progress. 11th November, 1949. For the first time in years the patient has now had a number of perfectly regular menses with a periodicity of 4–5/28 days. They have been associated with slight dysmenorrhoea. Her appearance is much more feminine than prior to the operation and the hirsutism is, if anything, slightly improved. She feels perfectly well and is mentally alert and no longer depressed.

August, 1952. The patient is still having perfectly regular menses. She is entirely feminine in appearance now, and the hirsutism is much improved.

Group 6. The Late Thecal Dominant Phase. (Type 3)

Characteristic Ovarian Microscopical Patterns: The ovaries at this stage exhibit only islands of theca cells scattered throughout the stroma. Follicles no longer occur.

Characteristic Endometrial Microscopical Patterns: The endometrium is completely atrophic.

Main Symptoms: (i) *Irregular Menses with Bouts of Amenorrhoea and Episodes of Menorrhagia*

Case 35. B.547. A.R., aged 48 years, married, para-3, gravida-4, was first seen at the Baragwanath Non-European Hospital on the 20th September, 1952.

Main Complaints. Irregular bleeding for the last few years with bouts of amenorrhoea of up to 3–4 months and episodes of haemorrhage for as long as 3–4 weeks. When admitted to hospital the patient was bleeding excessively.

Menarche at 14 years. The menses were perfectly regular until the episodes above described.

General examination. On abdominal palpation a freely mobile non-tender mass was felt arising out of the pelvis and extending up to the umbilicus.

Pelvic examination. The mass felt per abdomen was found to be continuous with the uterus and a diagnosis of myomatosis uteri was made.

Operation. 22nd September, 1952. The uterus was markedly enlarged being the site of numerous myomata. Both ovaries appeared small and atrophic with smooth capsules. A bilateral salpingo-oöphorectomy and total hysterectomy was performed.

Microscopical findings. (a) *Ovaries:* Sections of both ovaries exhibit only islands of theca cells scattered throughout the stroma (Fig. 35) and a number of corpora albicantia. These thecal islands vary in size from one to 20 or more cells. Neither developing, cystic nor atretic follicles are seen.

(b) *Endometrium:* Sections of the endometrium show it to be completely atrophic. Some of the glands are

small, round and tubular and tend to run parallel to the surface whilst others are grossly cystic (Fig. 36).

Conclusion. The patterns exhibited by the ovaries and endometrium are those of a hyperthecosis ovarii in the late thecal dominant phase (Type 3). The fact that a number of glands in the endometrium are cystic, suggests that at one stage this case was in the phase of cystic glandular hyperplasia but now as a result of marked thecal dominance has become completely atrophic.

Main Symptoms: (ii) *Marked Hirsutism and Complete Amenorrhoea*

Case 36. G.7577. J.B., aged 54 years, widow, para-1, gravida-1, was first seen at the Johannesburg General Hospital on the 21st June, 1949.

Main Complaints. Complete amenorrhoea for the past 27 years, marked hirsutism necessitating daily shaving, complete loss of libido since a young girl and diabetes for the last 12 years.

Menarche at 9 years. The menses were irregular from the onset being often profuse and watery. They remained irregular until the age of 24, when they began to diminish, completely ceasing at the age of 27 years.

Obstetrical history. The patient was married at the age of 22 years and fell pregnant soon afterwards. Although birth control was not practised following the birth of this child no further pregnancies resulted.

General examination. The patient had a masculine type of configuration, was markedly hirsute and had a marked temporal recession and patchy baldness of the hair on the head.

Pelvic examination. The clitoris was enlarged measuring ± 1 inch, the cervix and uterus were small and atrophied, and in the right adnexal region there was a firm mobile mass about the size of a pigeon's egg.

Operation. 8th August, 1949. A dilatation and curettage and left salpingo-oöphorectomy and right oöphorectomy was performed. The curettage failed to reveal any endometrium. The ovaries, which were round and enlarged to the size of golfballs, appeared to be entirely replaced by fibrous tissue.

Microscopical findings of ovaries. Sections of both ovaries exhibit numerous theca cell islands scattered throughout the stroma (Figs. 37 and 37a). Many of the cells in these islands are luteinized and it is possible to visualize their evolution from (Fig. 38) and reversal to (Fig. 39) ovarian connective tissue stroma. Neither primordial, developing nor atretic follicles are seen in the many sections examined.

Conclusion. The complete absence of endometrium on curettage and the pattern exhibited by the ovaries classify this case as a hyperthecosis ovarii in the late thecal dominant phase (Type 3). The fact that ovarian theca cells are still evolving from and reverting to the stroma suggests that a type of pituitary-ovarian cycle is still in existence in this case even although the uterus is apparently quiescent.

Progress. February, 1952. The hirsutism is now much improved. There are no longer any bald patches on the head and the temporal recession is very much less marked. The patient now shaves only once every 3 to 4 weeks instead of daily as was the case prior to operation. The clitoris, however, is still enlarged.

24th August, 1952. The patient has maintained her progress. Her libido is now perfectly normal.

10th September, 1953. The patient is very much more feminine in appearance now and the temporal recession of hair has completely disappeared. She is, however, rather ill from her diabetes.

Pure Theca Cell Tumour

Main Symptoms: Complete Amenorrhoea

Case 37. B.110. R.P., aged 35 years, married, nullipara, was first seen by the author on the 28th February, 1951.

Main Complaint. Complete amenorrhoea for the past 4 years.

Menarche at 12 years. The menses were perfectly normal until the age of 28 years when they started becoming irregular. Increasing episodes of amenorrhoea occurred and the libido decreased. The last menstrual period occurred in July, 1947 at the age of 31 years. At this time the patient was seen by a gynaecologist in England. His only positive finding was a negative gonadotrophin estimation.

General examination. Nil abnormal was detected.

Pelvic examination. The uterus was anteverted, small, and atrophic. It measured only $1\frac{1}{2}$ inches with the uterine sound. In the left adnexal region there was a firm, mobile mass about the size of an orange.

Operation. 6th March, 1951. At operation the mass in the left adnexal region was found to measure $3 \times 2\frac{1}{2} \times 2$ inches. The uterus was small and the right ovary atrophic. The mass was lobulated and on bisection bright yellow in colour. A left oöphorectomy was done.

Microscopical findings of tumour. Sections of the tumour show the typical pattern of a thecoma (Fig. 40). Although numerous sections were studied no area suggestive of granulosal elements was seen.

Progress. 21st June, 1952. The patient had her first menstrual period in the 5th post-operative week. Since then the menses have been regular with a periodicity of 3–5/26–28 days. The uterus has increased in size to $2\frac{3}{4}$ inches as measured with the uterine sound and the right ovary now appears to be of normal size. The libido is perfectly normal.

6th April, 1953. The menses are still perfectly regular and the uterus now measures 3 inches. No pregnancy has as yet occurred. However, there has been a great deal of domestic difficulty recently and this may account for it.

Discussion

The hyperthecosis syndrome, as can be seen from Table I, is essentially a condition of the second and third, and to a very much lesser degree, of the fourth and fifth decades of life. From an insidious beginning most frequently in association with, and probably as a result of,

persistent anovulatory cycles, in view of the continuous irregularity of the menses in the large majority of cases (Tables I, II, III), it runs a protracted course which may take anything up to 10, 15 or more years before it reaches its climax and in so doing completing its transformation of the human female into a masculinized, hirsute, sterile, often frigid individual with temporal hair recession, atrophied uterus and endometrium, and occasionally enlargement of the clitoris and atrophy of the breasts. During its course it passes through phases of irregular menses, menorrhagia and amenorrhoea, crowding of endometrial glands and pseudostratification of their cells, glandular intussesception, cystic glandular hyperplasia and endometrial atrophy. Even the phase of complete endometrial atrophy is not necessarily the final stage of this syndrome since, as will be shown in the following paper, adenocarcinoma of the corpus uteri itself may actually form the concluding chapter of this hyperthecosis syndrome. It will thus be seen that the so-called Stein-Leventhal syndrome merely forms a small facet, and not necessarily even the final facet, of this very large complex syndrome.

A feature of this condition, found in all our cases where this aspect was studied, is the usually low and at the most only slightly raised 17-ketosteroid levels, notwithstanding the presence of marked masculinization in some of these cases. Why this should be so can only be guessed at, at the moment. However, it does suggest that whatever the theca cell androgen may be it does not break down, as a rule, as does testosterone, into a 17-ketosteroid.

In view of what has previously been discussed regarding the histogenesis of the so-called arrhenoblastoma (Shippel, 1950c), it is important at this stage to compare the above 17-ketosteroid findings with those found in this type of ovarian tumour and the interstitial cell tumour of the testis, since if the arrhenoblastoma is an interstitial cell (Leydig cell) tumour of the ovary—arising from "elements of male differentiating potency left in the medullary portion of the ovary" during embryological development (Novak, 1944, p. 442)—as is the accepted concept—then it is logical to expect that its 17-ketosteroid findings will be as high as those found in interstitial cell tumours of the testis (Selye, 1947; Venning, 1942; Pessin, 1948; Sandblom, 1948; Newns, 1952). On the other hand, if the so-called arrhenoblastoma is in reality a mixed theca-granulosa cell tumour in which the granulosal element occurs in the form of either tubules or primitive cords (Shippel, 1950c) then the 17-ketosteroid findings should compare with those of the hyperthecosis syndrome.

This aspect of the arrhenoblastoma and the interstitial cell tumour of the testis has been studied by a number of authors. Talbot and Butler (1942), in their study of the 17-ketosteroid excretion in various endocrinological conditions, found that, whereas it was extremely high in adrenal cortical carcinoma, adrenal cortical hyperplasia and testicular interstitial cell tumours, it was within normal limits in the ovarian arrhenoblastoma. Thus they came to the conclusion that in virilized women and girls a very high 17-ketosteroid excretion meant that the patient had one of the two adrenal cortical diseases whereas a normal or slightly elevated 17-ketosteroid output was suggestive of the ovarian arrhenoblastoma.

Similar findings to the above have been recorded by Selye (1947), von Szathmary (1937), Mallory (1939), Kantor and Klawans (1940), Mallory (1941), Pedersen (1947), and Thomas *et al.* (1952). It is only in the very occasional arrhenoblastoma (Jones and Everett, 1946), and the odd case of polycystic ovaries (Alexander and Beresford, 1953) that the 17-ketosteroid excretions are found to be relatively high. Why this should be so in these random cases will only be answered when the theca cell androgen has been identified.

In itself the level of 17-ketosteroid excretion by the arrhenoblastoma as compared with that of the interstitial cell tumour of the testis is, perhaps, not of much significance. When, however, it is taken in conjunction with what has already previously been discussed regarding the histogenesis of the former tumour (Shippel, 1950c) it does strengthen the conclusions arrived at that the arrhenoblastoma is in reality a mixed theca-granulosa cell tumour, the masculinizing or non-masculinizing propensities of which are dependent upon the degree of thecal or granu-

TABLE I

Analysis of Cases

(Percentages in brackets)

No.	Age Distribution			Menstruation						Breast Feeding (months)				Hirsutism
	Up to 28 Years	29–40 Years	Over 40 Years	Average Age Onset Years	Irregular from Onset	Irregular Within 3 Years of Onset	Irregular Following Pregnancy: Abortion	Irregular Following Pregnancy: Full Time	Irregular After 40 Years	Irregular After Hypothyroidism etc.	Under 2	2–4	4–6	Over 9	
36	25 (69·4)	5 (13·9)	6 (16·7)	14·2	17 (47·2)	5 (13·9)	1 (2·8)	3 (8·3)	5 (13·9)	5 (13·9)	4	1	0	2	29 (80·6)
					22 (61·1)		4 (11·1)								

TABLE II

Analysis of Cases with Complete Menstrual Histories as Reported in the Literature

Authors Names	Journal	No. of Cases Reported	Menses Irregular from Onset	Irregular Within 3 Years of Onset	Irregular After 40	Irregular After Other Causes: Hypothyroidism	Schistosomiasis	Following Sterilization	Total
Ingersoll, F. M., and McDermott, M. V. (1950):	*Amer. J. Obstet. Gynec.*, **60**, 117	2	1	1					
Leventhal, M. L., and Cohen, M. R. (1951):	*Amer. J. Obstet. Gynec.*, **61**, 1034	5	3	1		? 1			
Culiner, A., and Shippel, S. (1949):	*J. Obstet. Gynaec. Brit. Emp.*, **56**, 439	3	2				1		
Shippel, S. (1950b):	*J. Obstet. Gynaec. Brit. Emp.*, **57**, 372	8*	2		4			2	
Stein, I. F., and Leventhal, M. L. (1935):	*Amer. J. Obstet. Gynec.*, **29**, 181	7	6					1	
Stein, I. F., Cohen, M. R., and Elson, R. (1949):	*Amer. J. Obstet. Gynec.*, **58**, 267	1	1						
Leventhal, M. L. (1941):	*Amer. J. Obstet. Gynec.*, **41**, 516	1	1						
Robinson, M. R. (1935):	*Amer. J. Obstet. Gynec.*, **30**, 18	7	6	1					
Total		34	22=64·7 Per cent	3=8·8 Per cent	4=11·8 Per cent	? 1	1	3	5=14·7 Per cent
			25=73·5 Per cent						

* Plus 1 case already mentioned under Culiner and Shippel (1949).

TABLE III

Summary of Total Number of Cases Reported in Tables I and II

	No. of Cases	Menses Irregular from Onset	Irregular Within 3 Years of Onset	Irregular Following Pregnancy	Irregular After 40	Other	Hypothyroidism	Diabetes	Pelvic Endometriosis	Schistosomiasis	Following Sterilization	Reticulo-Endothelial Stimulating Diseases (Rheumatic Fever)
TABLE I	36	17	5	4	5	5	1+?2	1	1	—	—	1
TABLE II	34	22	3	—	4	5	?1	—	—	1	1	—
Total	70	39=55·7 Per cent	8=11·4 Per cent	4=5·7 Per cent	9=12·9 Per cent	10=14·3 Per cent	1+?3	1	1	1	1	1
		47=67·1 Per cent										

losal—in the form of cords and tubules—activity respectively present. In this connexion it is further important to note that as with the hyperthecosis syndrome so also "a review of the literature shows that it is not uncommon for a patient with arrhenoblastoma to have a period of functional bleeding before developing amenorrhoea" (Jones and Everett, 1946).

Factors Associated with the Development of the Hyperthecosis Syndrome

By far the most common factor found in association with the development of this syndrome is, as can be seen from Tables I, II and III, a persistent irregularity of the menses commencing either at the menarche or within 3 years of the onset of menstruation. It is strange that this factor, although such a frequent occurrence (Table II), has never, as far as can be ascertained from the literature, given rise to much comment. Other apparent aetiological factors are in order of frequency, the anovulatory cycles which not infrequently begin to occur during the fifth decade of life, abortion or full time pregnancy, certain endocrinopathies such as hypothyroidism and diabetes, certain conditions such as rheumatic fever which tend to stimulate the reticulo-endothelial system, and, finally, local pelvic irritative conditions such as endometriosis, schistosomiasis and salpingitis and its sequelae. Irradiation of the pelvis, particularly when given in relatively small so-called sterilizing doses, may also play its part in the development of this syndrome.

The Pathogenesis of the Hyperthecosis Syndrome

(a) *As a result of anovulatory cycles during the second and fifth decades of life, hypothyroidism or diabetes*

Although it is impossible to present any definite proof that the irregularity of the menses in the cases above described was due to anovulation it can almost be taken from experimental evidence as a *sine qua non* that such was the case. This contention is strengthened, if strengthening is required, by the fact that the hyperthecosis syndrome may also develop, on the assessment of our limited material, as a result of hypothyroidism or diabetes, conditions which, according to the respective observations of Gillman and Gilbert (1953) and Hamblen (1945), usually result in anovulatory cycles. It is felt, that as more and more of the above two endocrinopathies are observed they will be found to be relatively common factors in the development of the hyperthecosis syndrome.

One of the most important factors in the development of this syndrome would appear to be, therefore, persistent anovulatory cycles extending over a prolonged period of time. As a result of this failure to ovulate and, therefore, the intervention of the corpus luteum phase, a phase of relative rest and even of regression for the remaining structures of the ovary, the ovarian stroma and follicles endure protracted stimulation by the pituitary. This not only results in the development of a large number of follicles with their zones of granulosa and theca, but the stromal cells, particularly those contiguous with the thecal elements, are also stimulated and changed into protheca, the probable precursors of the theca cell. In a similar manner the tunica—also a mesenchymal derivative as are the stromal and thecal elements (Shippel, 1950a)—is probably stimulated. Thus an ovary consisting of a thickened tunica, numerous follicles at all stages of development and zones of protheca, results. The thickened tunica is, therefore, not the cause of the large number of follicles in the ovary by setting up a blockade, as is the accepted concept (Leventhal, 1941), but develops rather *pari passu* with, and results from, a similar stimulus to that of the follicles.

As will be brought out in the discussion below, the primary aetiology of this syndrome is not abnormal or excessive pituitary stimulation of the ovaries—the usually accepted explanation—but rather factors inherent in, or locally irritative to, the ovaries, or lacking from other members of the endocrine system. Otherwise it would be logical to expect that the results of treatment, focused as this is on the ovaries—wedge resection—instead of the pituitary, would be as evanescent as those initially achieved by Hercules on the Hydra of Lerna, the many-headed monster whose heads grew again the moment

they were decapitated. Nor could the excellent results of non-recurrence in 75 cases followed up for over 15 years (Stein, Cohen and Elson, 1949) have been possibly attained.

As the hormone production of the ovarian follicles increases so pituitary function is depressed. This inverse relationship between the ovarian and pituitary functions results in phases of follicular stimulation and follicle depression and atresia. During these latter phases, as is usually the case with follicular atresia, some thecal hyperplasia may occur and if the number of follicles undergoing atresia are moderately numerous then the amount of ovarian thecal activity resulting may be fairly marked.

Those follicles which do not undergo atresia, on the other hand, probably grow larger with each phase of pituitary stimulation until ultimately, as a result of distortion and straightening of their arterioles and consequential increases in intra-arteriolar and capillary pressures, intrafollicular transudation of fluid occurs (Delson, 1949) with resultant pressure atrophy of the granulosa and inanition of the theca. It is probably for these reasons that the amount of granulosa and theca present in cystic follicles is usually limited. With the destruction of these follicles the amount of gonadotrophin per phase of pituitary activity used up in their stimulation now probably becomes either partially or wholly available for the stimulation of a fresh group of primordial follicles and further stimulation of the theca and protheca already present. However, as this theca increases so does its capacity to depress the pituitary increase with the result that the amount of gonadotrophin necessary for the stimulation of primordial follicles to maturity slowly becomes unattainable. With the advance of this syndrome, therefore, less and less mature follicles appear in the ovaries and the chances of ovulation occurring become thus extremely remote.

By these means, prothecal development and its transformation into theca, follicular atresia or cystic degeneration, and the blighting of maturing follicles in their earlier stages of development, the theca slowly and imperceptibly but relentlessly increases at the expense of the granulosa and the ovary passes from the phases of thecal-granulosal synergism into those of thecal dominance. These processes may take years to accomplish unless speeded up by factors such as ageing of ovaries with resultant failure of follicle development, or pregnancy or abortion, the mechanisms of which will be discussed below.

There thus exists in this syndrome an inverse relationship between the theca and granulosa which, within the limits of biological possibility, may be equated in the formula $ab=K$ where "a" stands for granulosal, "b" for theca and "K" for constant; a constant which although variable in different persons is probably relatively stable, within biological limits, in a particular individual.

Thus the condition of hyperthecosis ovarii becomes, as it progresses into the later phases, an irreversible process unless rectified by either operative or endocrine means; the former entailing the removal of most of the theca by ovarian wedge resection, and the latter by causing a complete depression of pituitary gonadotrophin production for a sufficient length of time to allow for involution of the excessive thecal element to occur.

Finally in those cases which persist into or only begin to develop during the fifth decade or later in life, a period in which normally the ovary becomes more and more resistant, or incapable of responding, to pituitary stimulation, follicles cease to mature (Case 30) and an ovary consisting of only islands of theca cells and stroma results (Cases 35 and 36). It is probably in this manner that these features, found usually in the ovaries of patients afflicted with adenocarcinoma of the corpus uteri, eventuate. However, this aspect will be discussed in greater detail in the following paper.

Notwithstanding the depressive hold the excessive theca has on the pituitary, odd, very infrequent freak ovulations may occasionally still occur and, depending upon the state of the endometrium at this time, pregnancy may result and either go to term or abort. However, if the endometrium is completely depressed and atrophic, as in Case 33, the chances of pregnancy obviously become remote even although there has been ovulation. Thus this syndrome would appear to be an aetiological factor in some cases of repeated abortion.

The above observations suggest that the contention that most children have persistent anovulatory cycles during their first 2 to 3 years of menstruation is incorrect; otherwise the hyperthecosis syndrome would be an extremely common condition. One agrees, therefore, with Novak (1944, p. 75) when he says "there is no doubt that in many, and probably the great majority of girls, ovulation occurs from the first menstrual cycle, and that the very first menstrual bleeding is preceded by a first ovulation". This being so, then it is logical to conclude that those cases of hyperthecosis ovarii described earlier, whose menses although regular at first became irregular within their first 3 years of onset, were probably anovulatory from the start since "typical and periodic menstrual bleeding can occur without ovulation" (Novak, 1944, p. 71).

Why it is that a small percentage of individuals commence their sex phase of life with anovulatory cycles and so incur the risk of developing the hyperthecosis syndrome is a problem still requiring investigation. It may be that the ovaries in some individuals at this age have not reached a sufficient degree of maturity to be capable of responding to the luteinizing hormone of the pituitary; or it may be that other members of the endocrine system, such as the thyroid or ? pancreas or other gland, are not sufficiently mature to assist the ovary with ovulation; or perhaps even the pituitary in some of these cases, just as is the case in the postmenopausal period of life, is only capable at this stage of producing a gonadotrophin which has a predominantly follicle-stimulating effect. Whatever the cause may be, and it would appear to be a hypofunction of one or a number of different endocrine organs rather than hyperfunction of the pituitary, the chances are that by the time the fault or faults have rectified themselves, and rectify themselves they probably do in the large majority of cases, the ovaries have been safely launched on their abnormal and irreversible course. It becomes obvious therefore, that the concept of a pituitary–ovarian, or pituitary–thyroid, or pituitary–any-other-gland axis is in this day and age an anachronism. Thus the sooner we divorce ourselves from this concept the sooner will we solve the many problems still awaiting solution.

(b) *As a result of pregnancy*

The initiation of the hyperthecosis syndrome through pregnancy appears to be dependent upon a number of factors, the most important of which are on the basis of our present observations (*a*) the degree of hyperthecal activity present in the ovaries at the end of gestation, (*b*) the duration of lactation, (*c*) the time interval between parturition and the recommencement of menstruation, (*d*) whether menstruation recurred during the period of lactation and finally, pending confirmation of the very recent observations of Danowski *et al.* (1953), whether there has been a phase of relative hypothyroidism following the pregnancy.

The availability of material for the study of the changes occurring in human ovaries during pregnancy is obviously very limited. However, it would appear from observations on a number of ovarian biopsies obtained from patients requiring Caesarean section and sterilization at term, that marked thecal activity (Figs. 41 and 42) is not an uncommon feature of the ovaries at this stage. Whether this thecal response is a frequent occurrence, and whether it is important in the economy of pregnancy obviously requires further study. Nevertheless, it probably does account for the aggravation of the hirsutism which occurred in Case 11 during her pregnancy. The actual cause of this ovarian response is of no import in the present discussion. However, it seems, on the basis of the experimental observations of Selye and Collip (1933), Geist, Gaines and Salmon (1941), and Greenblatt (1941), to be a passive result of the large amount of circulating chorionic gonadotrophin present during this period. Thus at the end of gestation the ovaries, in at least some cases, are left with the legacy of a large amount of theca; a legacy which, unless it is lost through post-partum involution of the ovaries, an involution best assisted by lactation (Udesky, 1950), may actually initiate the hyperthecosis syndrome in that individual.

A failure to lactate and an early recurrence of menstruation (Sharman, 1951) will, therefore, find the ovaries, if they are the site of thecal hyperplasia, unprepared for and incapable of coping with the new phase of menstrual activity. This is, therefore, one method whereby the process of pregnancy, unless followed to its

logical conclusion with lactation, may actually initiate the hyperthecosis syndrome. In view of this it is most unfortunate that a trend is developing in modern young mothers to leave the feeding of their infants to the bottle rather than the breast. However, even the lactating mother is not quite free of the risk of developing this syndrome. But probably the risk is far less than under the previous circumstances since, if menstruation should recur during this phase of lactation, there is, on the basis of Udesky's (1950) observations, an 80 per cent chance of her menses being anovulatory. Thus not only may there be a restimulation of the thecal elements in these cases, *depending on how soon postpartum the menses recommenced and, therefore, how depressed these elements have been allowed to become*, but if the patient should go on breast feeding and, therefore, having anovulatory cycles, she may actually speed up the development of this hyperthecosis syndrome, particularly if the ovaries were the site of marked thecal activity and the menses recurred soon after the termination of pregnancy. If, however, there has been no recurrence of menstruation during a period of about 6-months lactation then on our observations it would appear that the chances of this syndrome developing are almost nil. One of the probable reasons, therefore, for the development of this syndrome in Cases 22 and 28, notwithstanding their prolonged periods of lactation, is the recurrence during this period of menses which were probably anovulatory (Udesky, 1950) and which in Case 28 occurred for the last 9 months of this phase. It may also be that in Case 22 there had been, in addition, incomplete involution of the thecal elements when the menses recommenced, since from her menstrual history the patient was obviously heading for the hyperthecosis syndrome prior to her chance pregnancy and must, therefore, have built up quite a store of the thecal element in her ovaries.

It is unfortunate that as yet we have no knowledge as to why some women remain amenorrhoeic during this period of lactation whilst others start menstruating again, nor as to what period of lactation is necessary for the complete involution of the thecal elements to occur.

From all the above observations it would appear, therefore, that patients suffering from this syndrome are likely to cure themselves of this condition if they should manage to fall pregnant, carry to term and following delivery lactate for, and remain amenorrhoeic during, a period of approximately 6 months. On the other hand, cases who abort or who after carrying to term fail to lactate or start menstruating during the period of lactation may actually accelerate the progress of the disease.

Although on the surface and on the basis of our limited amount of material it would appear that a failure to lactate is not as serious a problem as depicted above, yet it is felt that if many of the cases of amenorrhoea, menorrhagia, endometrial hyperplasia and masculinization were carefully traced to their origin they would be found to date from a miscarriage, or pregnancy where there had been no, or only a very short period of lactation, or where menstruation had recurred relatively early, during the phase of breast feeding. The growing practice of leaving the feeding of the child to the bottle and patented milk products rather than the breast must, therefore, be seriously condemned.

It is also important to note that, if the ovaries happened to have been the site of fairly marked thecal activity at the termination of pregnancy, and the patient had failed to lactate or had lactated for only a short period of time, then the longer she waits before trying to fall pregnant again the more likely is she to develop sterility and the more absolute is likely to become this state, since the longer she waits the more powerful becomes the grip of the thecal element on the ovaries and the less likely becomes the possibility of the odd ovulation.

Finally, if the observations of Danowski *et al.* (1953) are correct, that there occurs following pregnancy a period of relative hypothyroidism, we have yet another factor capable of initiating the hyperthecosis syndrome as a result of gestation.

(c) *As a result of conditions which tend to stimulate the reticulo-endothelial system*

In his studies of the effects of trypan blue injections in animals, a dye which tends to stimulate the reticulo-endothelial system, Gillman (1953) almost invariably found, *pari passu*

with its response, a thecal response in the ovaries even to the extent of theca-cell tumour formation. It would thus appear that under certain circumstances and conditions such as rheumatic fever (Case 27), the theca-cell, a mesenchymal derivative (Gillman, 1948), is capable of responding as a member of the reticulo-endothelial system and in so doing may actually set the ovaries on the course of the hyperthecosis syndrome. Whether this particular type of thecal response is a common cause of this syndrome in human beings it is difficult to say, but it would appear, from our limited material, to be fortunately one of the rarer aetiological factors.

(d) *As a result of local pelvic irritative conditions such as endometriosis, schistosomiasis, salpingitis and its sequelae, and perhaps pelvic irradiation*

Because of its stromal origin (Gillman, 1948) and its ability to respond as a member of the reticulo-endothelial system (Gillman, 1953), it is possible for the theca cell to be activated in any pelvic inflammatory condition, especially of the chronic type where there normally occurs a marked mesenchymal reaction. Furthermore, as follicles and granulosa cells are destroyed and damaged by the chronic inflammatory processes and advancing fibrosis in ovaries directly involved in the above lesions, and they are involved in most cases of salpingitis and a very high percentage of endometriosis cases (Fallas, 1951—78 per cent; Stearns, 1952—63 per cent), more pituitary gonadotrophin becomes available for the further stimulation of the thecal elements and the changing of stromal cells into prothecal and ultimately theca cells. Thus slowly, unless completely destroyed by the process of fibrosis —a most unlikely possibility—the ovaries may be steered in the direction of the hyperthecosis syndrome and its resultant endometrial and menstrual anomalies. This is the probable reason for the menstrual abnormalities, particularly menorrhagias, found in cases of schistosomiasis (Charlewood, Shippel and Renton, 1949) and so frequently in cases of salpingitis, and for the oft-occurring association between endometriosis and endometrial hyperplasia (Alves de Lima, 1950–1951), cystic glandular hyperplasia and so-called functional bleeding; a feature which occurred in 88·3 per cent, 74·8 per cent and ±75 per cent of the cases of endometriosis respectively reported by Counseller and Crenshaw (1951), Stearns (1952), and Bennet (1953).

Whilst on the subject of endometriosis it is important to direct attention to certain important differences which become manifest between external endometriosis and adenomyosis (internal endometriosis) on the basis of the above observations. Although of similar pathology, consisting as they do of ectopic endometrium, their aetiology and pathogenesis would appear to be different, since, whereas pelvic endometriosis may initiate the hyperthecosis syndrome, adenomyosis is probably frequently the result of this syndrome arising, as it often does, from hyperplastic endometria (Novak, 1952); the type of endometrial pattern present during the later synergistic phases of this condition. This would explain the frequent association between pelvic endometriosis, hyperplastic endometria such as cystic glandular hyperplasia, and adenomyosis. However, it is also possible for adenomyosis to occur in the absence of endometriosis if the initiating agent of the hyperthecosis syndrome happens to be one of the other factors already described.

It also becomes obvious from the above observations why sterility is such a frequent concomitant of endometriosis even although the Fallopian tubes are usually patent (Novak, 1944, p. 470; Everett, 1952), or why, probably as a result of the depressed state of the endometrium in the later phases of the hyperthecosis syndrome, there is such a high incidence of spontaneous abortion with endometriosis in the odd case of chance pregnancy (Counseller and Crenshaw, 1951; Bennett, 1953).

To summarize at this point then, there are, according to our present observations 4 main groups of factors responsible for the initiation of the hyperthecosis syndrome in the human female. By far the most common is that associated with persistent anovulation commencing either during the second—frequently from the menarche—or fifth decades of life, or as a result of certain endocrinopathies such as hypothyroidism or diabetes. The second group is the result of pregnancy where there has occurred

a marked thecal response in the ovaries and the patient has either failed to lactate or has started menstruating again rather early during the period of lactation. The third group is due to conditions which tend to stimulate the reticulo-endothelial system of which the theca cell under certain circumstances appears to be a member, and finally the fourth group is that associated with local pelvic irritative conditions such as schistosomiasis, endometriosis, salpingitis and its sequelae, and perhaps pelvic irradiation.

In conclusion, therefore, it becomes obvious, on the basis of all these observations, that contrary to the generally accepted concept, the pituitary plays no role in the actual initiation of the hyperthecosis syndrome, and very little part, except indirectly, in its progress.

Diagnosis

Because the condition of hyperthecosis ovarii is only one of a number of syndromes capable of causing masculinity in the human female it is essential that the patient be thoroughly investigated before being subjected to surgical interference. Unfortunately this is an aspect rather frequently neglected by the more radical surgeon.

Hirsutism in itself is of very little significance in the diagnosis of the hyperthecosis syndrome or of any of the other masculinizing syndromes since, contrary to popular belief and acceptance, some degree of hairiness of the face and lips, even to a moderately marked degree, is such a frequent occurrence in otherwise perfectly normal women that it has to be considered a normal variant. Hirsutism plus some enlargement of the ovaries, even if demonstrated radiologically according to the technique of Stein (1945), is also not sufficient evidence for a diagnosis of this syndrome since in the odd very occasional case as described by Bergstrand (1934) this picture may occur as the result of a basophilic adenoma of the pituitary. In this particular case ". . . The ovaries were enlarged and yellowish. There were many atretic follicles with perifollicular zones of luteinized theca cells. At autopsy a large basophilic adenoma of the pituitary gland and diffuse hyperplasia of the adrenal glands were found." Thus, in cases of primary hypophyseal hyperfunction, fortunately a rather rare disease, the possibility of simultaneous ovarian and adrenocortical hyperactivity must always be borne in mind. Before making a diagnosis of the hyperthecosis syndrome, therefore, it is essential:

(1) That a very careful menstrual and obstetrical history be taken on the lines already indicated.

(2) That the previous medical and gynaecological histories be investigated with particular reference to hypothyroidism, diabetes, pelvic infection, schistosomiasis, endometriosis and reticulo-endothelial stimulating diseases.

(3) That the patient be examined in the nude for general configuration and muscular build and, if any tendency towards adiposity, plethora and hypertension be found, that the possibility of Cushing's disease be ruled out.

(4) That the external and internal genitalia be carefully examined for size of clitoris and uterus and size and consistency of ovaries.

(5) That endometrial biopsies be studied and, finally,

(6) That the 17-ketosteroid and corticosteroids, the latter a feature unfortunately not examined in our cases, be investigated since if raised they are more suggestive of adrenocortical hyperactivity than of the hyperthecosis syndrome.

The importance of endometrial studies in the diagnosis of this syndrome cannot be stressed enough. However, it must be understood, that the endometrial patterns already described are merely landmarks in the progress of the disease and that because we are here dealing with a dynamic process there must of necessity be a great deal of endometrial, although not necessarily ovarian, pattern repetition even though the main trend is ever forward, sometimes slowly and sometimes rapidly with, in the latter case, often the omission of a phase or phases, towards the late thecal dominant stages and their resultant clinical manifestations. Thus, whereas an endometrium removed immediately prior to the onset of a bout of menorrhagia may show cystic glandular hyperplasia, one obtained soon after the cessation of this bout of bleeding may only exhibit a normal early proliferative pattern, simply because insufficient time has elapsed for the change to cystic glands to have occurred. It may be necessary sometimes, there-

fore, for a number of endometrial biopsies to be studied, preferably removed some time after the cessation of a bout of bleeding, before any decision can be reached regarding the presence of the hyperthecosis syndrome. Nor is it safe to draw any final conclusions from the endometrium if only a single feature such as pseudostratification, crowding of glands, or glandular intussusception is present. Only when a number of these components occur together, or, if singly, if they tend to vary in a number of consecutive biopsies, are they of consequence. However, if the single feature happens to be cystic glands it is significant. (The place of hyperoestrogenic activity in the production of cystic glands has already been discussed in a previous paper; Shippel, 1950b.) On the other hand, if the endometrium is completely atrophic, its usefulness as a diagnostic aid becomes very limited unless it exhibits some cystic glands or the patient shows other stigmata of the hyperthecosis syndrome. To recapitulate, therefore, it is essential that an accurate diagnosis be first made before the knife is resorted to, otherwise failures are likely to occur and the operation of ovarian wedge resection, such an excellent operation in the right case, is likely again to pass into oblivion and disgrace.

Treatment

The basis of treatment in the hyperthecosis syndrome, whether it be by operative or endocrine means, is not the removal of the thickened ovarian tunica and resulting cyst blockade (Leventhal, 1941) as is the accepted idea, but rather the elimination or depression respectively of the excessive amount of theca present. By these means it becomes possible to release the pituitary from the thecal stranglehold and grant the ovaries the ability to respond normally to its gonadotrophins. The follicles will now no longer be blighted in their earlier stages of development and will thus be able to reach full maturity even to the stage of ovulation.

The actual technique of ovarian wedge resection has been amply demonstrated by Stein (1945) and thus does not require repetition here. Suffice it to say that the aim of the operation is the removal of as much as possible of the theca and follicular cysts present, whilst at the same time leaving sufficient cortex and primordial follicles for the normal functioning of the ovaries.

Notwithstanding the excellent results obtained with ovarian wedge resection in the treatment of the hyperthecosis syndrome, it is felt that the future therapy lies in the direction of endocrinological depression of pituitary gonadotrophin production for a sufficient length of time to allow for involution of the theca to occur without at the same time jeopardizing the recovery of the ovaries.

This is the probable reason for the excellent results obtained by Karnaky (1944) with his prolonged oestrogen therapy in the treatment of cystic glandular hyperplasia—a phase of the hyperthecosis syndrome—a treatment unfortunately held in derision by most gynaecologists by whom the aetiology of this disease has been sought in ovarian hyperoestrogenic activity.

Physiological as this latter form of therapy might be, however, it is felt that, until we have (*a*) more accurate and less laborious methods for assaying gonadotrophin, since unless it is completely depressed the theca is still capable of activity, (*b*) a better knowledge as to the optimum period of therapy necessary for complete thecal involution to occur without at the same time entailing any risk to the recovery of the ovaries, and (*c*) some experimental evidence as to the best hormone or hormones to use for the purpose, it would be folly to adopt this form of therapy universally.

Prognosis

The prognosis as regards a return to normal menstruation, ovulation and possible pregnancy following ovarian wedge resection, is dependent to a very large degree upon what the primary aetiological factor was in the initiation of this hyperthecosis syndrome. In the case of hypothyroidism the outlook is good provided the patient is permanently maintained on thyroid therapy. Failing this, on the basis of Gillman and Gilbert's (1953) observations, anovulatory cycles will recur and the patient's ovaries will once more be forced to follow the abnormal course of this condition.

With diabetes, on the other hand, it is difficult to prognosticate at the present stage of our

knowledge, since, although we have evidence to suggest (Hamblen, 1945) that the incidence of pregnancy in diabetic women has been increased by only 10 to 15 per cent as a result of insulin therapy, thereby suggesting that many of these cases persist with their anovulatory cycles in spite of this treatment, we do not know whether this failure to ovulate is due to a lack of some other factor in the diabetic milieu or due to the fact that the ovaries of many of these cases had already been committed to the hyperthecosis syndrome when the insulin therapy was instituted.

In hyperthecosis ovarii resulting from endometriosis, a pathology which it is nigh impossible to eradicate except through ultra radical means or X-ray sterilization of the patient, the prognosis is poor. If, therefore, an ovarian wedge resection be done on such a case primarily for sterility, it is advisable that the patient try to fall pregnant as soon after the operation as possible, for the longer she waits the greater are the chances of a recurrence of the syndrome. With schistosomiasis, on the other hand, the outlook today is good since with our modern drugs it is possible to eradicate this disease.

Finally it is obvious that, as the result of a pregnancy, or the subsequent development of any of the hyperthecotic aetiological factors or, in extremely rare cases, the persistence of an ovary incapable of responding to the pituitary luteinizing hormones—that is if such an entity exists—the whole syndrome of hyperthecosis ovarii may be rekindled in patients already operated upon for this condition.

It is thus possible, following ovarian wedge resection in these cases, to give a prognosis regarding a return to normal menses, ovulation and possible pregnancy. It is, however, not possible to do so with regard to the hirsutism since the degree of hairiness exhibited by the patient seemingly bears no relationship to the phase reached in the syndrome, and, therefore, to the quantity of circulating thecal androgen, but rather to the sensitivity of the hair follicles to this latter hormone. It would further appear that at least in some cases the hair follicles once roused from their inactivity are capable of maintaining their function without any further recourse to stimulation. It is probably for these reasons that cases in the later phases of the hyperthecosis syndrome may exhibit no hirsutism and in the earlier phases a marked degree, and that, following treatment, the hirsutism may improve a great deal or hardly at all. This latter feature has been used by some as a criticism against the ovaries being the *causa vera* of this syndrome. However, in contradistinction to this opinion a similar relationship is found to exist between the testis and masculine hirsutism. Thus ". . . in postpubertal eunuchs beard and pubic hair growth may remain normal throughout life" (Selye, 1947) and ". . . in the adult fully developed man excision of the testicles usually causes relatively few deficiency signs and hardly alters the secondary sex attributes" (Zondek, 1944).

Finally, it is interesting to note that, whereas cortisone is capable of alleviating very rapidly the hypertrichosis of adrenocortical hyperactivity, it had absolutely no effect in the one case of our series of hyperthecosis ovarii (Case 12) where this form of therapy was tried. Conclusions can obviously not be drawn from a single case, but if with further experimentation this proves to be the rule, and on theoretical grounds there appears to be no reason why this should not prove to be so, then we have here yet another method for differentiating between the hyperthecosis syndrome and adrenocortical hyperactivity.

The Ovarian Theca Cell Tumour

So strong has been the hold of traditional thought upon most gynaecologists and gynaecological pathologists concerning the ovarian theca cell tumour, that, even though the thecomas they (Diddle and O'Connor, 1951) were discussing exhibited androgenic propensities, they still classified them under the heading of feminizing ovarian tumours. Yet more and more evidence is accumulating to show that the theca cell tumour is often masculinizing (Traut and Marchetti, 1940; Blackmun, 1942; Stout, 1946; Patton and Patton, 1948; Reycraft, 1949). Such was the case with the tumour herein described (Case 37); a tumour which caused persistent amenorrhoea for more than 3½ years and so depressed the uterus that it measured only 1½ inches with the uterine sound.

Although it is impossible at the present stage of our knowledge to say whether any relationship exists between the histogenesis of the hyperthecosis syndrome and the theca cell tumour, certain features are, nevertheless, common to both pathologies. Thus, as is usually the case with the thecoma (Traut, Kuder and Cadden, 1939; Traut and Marchetti, 1940; Novak, 1952), the ovaries at all phases of this syndrome, except the late thecal dominant phase (Type 3), exhibit both thecal and granulosal elements, and as with the thecoma the ovaries of Cases 25 and 33 show large areas of hyalinization.

It is contended, therefore, on the basis of the observations in this study, that the pure thecoma is a masculinizing tumour, but, as a result of admixtures of various ratios of granulosa cells, may produce endometrial patterns ranging from cystic glandular hyperplasia to complete atrophy and menstrual abnormalities from menorrhagia to amenorrhoea.

The exact nature of the theca cell hormone still requires investigation and an attempt in this direction is being made in this University. However, on the basis of the present study it would appear to be an androgen incapable, as a rule, of breaking down into a 17-ketosteroid, and with a chemical structure probably closely related to desoxycorticosterone (Cuyler, Ashley and Hamblen, 1940), and more closely to progesterone than is testosterone, in view of the large quantities of pregnanediol (Leventhal and Cohen, 1951) often excreted in the urine of patients with this syndrome.

In conclusion, it is important and interesting to note that Grody, Lampe and Masters (1953) in attempting to establish in menopausal patients the "optimum dosage levels of oestrogen and androgen in combination, such that the greatest desirable effects of oestrogen could be attained with concomitant development of atrophy of the endometrium and of the vagina" inadvertently produced by varying their oestrogen-androgen ratios the same range and sequence of endometrial gland patterns—glandular intussusception, cystic glandular hyperplasia and endometrial atrophy—as described in this paper. Experimental evidence thus, accidentally and unexpectedly stumbled upon, confirming all that has been discussed and suggested regarding the hyperthecosis syndrome.

Summary

From an analysis of the clinical histories, and study of the ovaries and endometrium of 37 cases it has been possible to demonstrate the probable aetiology and pathogenesis of the hyperthecosis syndrome and its resultant progressive clinico-endometrial pattern variations.

For the sake of clarity the syndrome has been divided into 6 phases—the first 3 being those concerned with thecal-granulosal synergism and the last 3 with thecal dominance—and the characteristic ovarian and endometrial patterns for each phase have been described.

During its protracted course of 10, 15 or more years the syndrome is shown to pass through phases of irregular menses, menorrhagia and amenorrhoea, crowding of endometrial glands and pseudostratification of their cells, glandular intussusception, cystic glandular hyperplasia and endometrial atrophy, and in so doing transforming the human female into a masculinized, hirsute, sterile, often frigid individual with temporal hair recession, atrophied uterus and endometrium and occasionally enlargement of the clitoris and atrophy of the breasts.

Evidence is presented to show that the primary aetiology of this syndrome is not abnormal or excessive pituitary stimulation—the usually accepted explanation—but rather factors inherent in, or locally irritative to, the ovaries, or lacking from other members of the endocrine system.

Four main groups of factors have been found to be responsible for this syndrome. By far the most common is a persistent anovulation either from the menarche or commencing within a few years of its onset or after the age of 40, or as a result of hypothyroidism or diabetes. The other aetiological factors are pregnancy, conditions which tend to stimulate the reticuloendothelial system and, finally, local pelvic irritative conditions such as schistosomiasis, endometriosis and salpingitis and its sequelae.

The pathogenesis and prognosis of the hyperthecosis syndrome as a result of each of the

above factors are discussed and the methods of diagnosis and treatment are given.

Finally on the basis of the above study an explanation is offered as to why on occasions the theca cell tumour exhibits masculinizing propensities and at other times is associated with feminizing manifestations.

I wish to express my sincere thanks to Professor O. S. Heyns for his interest and encouragement shown in the preparation of this paper, to Dr. A. Culiner for his very helpful criticism of the manuscript and to my many colleagues who by submitting to me their operative material and very detailed histories of their cases, and often even their patients, made this study possible. I wish also to thank Mrs. A. S. du Pisanie for the great trouble she went to in the typing of the manuscript and Mr. J. I. van Niekerk for his very valuable assistance with the photomicrography.

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THE EXCRETION OF CHORIONIC GONADOTROPHIN IN NORMAL PREGNANCY AND IN WOMEN WITH HYDATIDIFORM MOLE

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INTRODUCTION

IT has been shown that women with hydatidiform moles excrete abnormally large amounts of chorionic gonadotrophin (C.G.) (Zondek, 1929; Aschheim, 1930). For this reason dilution tests have been used to distinguish a pregnancy from a mole or chorionepithelioma. Zondek (1931) suggested that a level of 50,000 "mouse units" or more of gonadotrophin per litre of urine, an amount normally sufficient to produce a positive reaction when injected in a dilution of 1 in 100, indicated the presence of either a mole or chorionepithelioma. Despite evidence to the contrary, there is still a general impression that urines from patients with such abnormalities of the chorioplacental system will always give a positive "pregnancy test" in a dilution of 1 in 100, a view held by some clinicians and pathologists. It is now well established that not only may the level of C.G. excreted during a normal pregnancy be more than 50,000 mouse units but also weakly positive and even negative biological reactions may be obtained with urine concentrates from molar and epithelioma cases (Hobson, 1952).

Although information is available about C.G. excretion in molar and epithelioma cases, few of the data are comparable, most reports emphasizing clinical and pathological aspects of the cases. Where quantitative assays have been made the results are expressed in "animal units". The only comprehensive investigation is that of Hamburger (1944), one of the few workers to express his findings in International Units, despite the availability of an International Standard Preparation since 1939.

That biological tests are only occasionally of diagnostic value is perhaps due to the lack of comparable information about C.G. excretion in hydatidiform mole, chorionepithelioma and pregnancy. This lack of knowledge is understandable when the infrequent occurrence of moles, variously estimated as 1 in 2,500 pregnancies (Novak, 1952), 1 in 2,334 (Sherman, 1935), or 1 in 1,300 (Cosgrove, 1938), and the even rarer occurrence of chorionepithelioma is remembered. Because of the difficulties of obtaining such material few workers have been able to assay the C.G. in body fluids from a large number of cases. This department has such facilities, for in addition to doing many thousands of "pregnancy" tests we also do about 1,000 semi-quantitative estimations annually. Semi-quantitative estimations or dilution tests are usually asked for when the presence of a mole is suspected. The results of these tests, together with the case history of the patient, may be used by the clinician in an attempt to differentiate between doubtful pregnancy and a possible pathological condition. The purpose of the following investigation, based largely upon material obtained during routine testing, has been to provide precise information regarding urinary C.G. excretion from a large number of patients with hydatidiform mole, and to compare C.G. levels with those obtaining at all stages of pregnancy.

MATERIALS AND METHODS

The present material was selected from routine dilution tests done during the last 2½ years. A

total of 1,982 specimens were examined, for which the provisional diagnosis was hydatidiform mole or chorionepithelioma. A questionnaire, following each test, requested the clinical diagnosis and other information pertinent to the investigation. The data presented here are obtained from 105 patients with hydatidiform mole and are additional to 16 cases published recently (Hobson, 1952). A further 100 mole cases are not described here because the clinical information was incomplete. For comparison dilution tests were also done on urines obtained between the 3rd and 40th week of pregnancy.

To determine the amount of C.G. in urines sent for examination, two biological techniques were employed; the Hogben dilution test (Hobson, 1952), and bio-assays using groups of male *Xenopus laevis* (Hobson and Landgrebe, 1954). In the majority of cases urinary C.G. values were obtained by the dilution method, dilutions most commonly used being 1 in 10 and 1 in 100, although in some cases intermediate and higher dilutions were performed. It is common laboratory practice to give the results of semi-quantitative tests as being positive or negative to the particular dilution employed. Providing the sensitivity of the test animal to C.G. is known, it is perfectly feasible to express the amount of C.G. present in the urine in International Units per litre as urines containing approximately 3,000 or more I.U. C.G. per litre give a positive Hogben test (Hobson, 1952). It follows therefore that positive responses from specimens diluted 1 in 10 and 1 in 100 will not contain less than 30,000 and 300,000 I.U. per litre respectively. When the level of gonadotrophin falls below 3,000 I.U. per litre of urine, the test is usually negative. The response to C.G. of both male and female Xenopus was checked at regular intervals with a standard preparation. Throughout this investigation estimations were carried out on first morning specimens of urine and values obtained expressed in I.U. C.G. per litre.

Mole tissue was obtained from 7 of the patients. This was placed in acetone of analytic quality soon after removal. After complete homogenization in fresh ice cold acetone the tissue residue was filtered off and placed in a desiccator until dry. This material was ground up in a mortar with freshly made ice cold distilled water and was stirred for 10 minutes at 2,000 r.p.m. The residue was centrifuged off and extracted as before, the supernatant fluids from both extractions were combined, and the pH of the solution adjusted to 4·0 with glacial acetic acid. The gonadotrophin was precipitated from the supernatant fluid by the addition, with stirring, of 5 volumes of ice cold acetone and 1 volume of ice cold ether and the precipitate allowed to develop overnight in a cold room at 5° C. The precipitate so formed was collected in a Seitz filter, washed with acetone and dried. The dry powder was ground and kept in a desiccating cabinet until required. For comparison 2 full-time placentae were extracted and prepared in exactly the same way. Before assaying, the precipitates obtained were dissolved in distilled water and the dose to be injected contained in 1 ml. Extracts were freshly made up before each assay and the potency expressed in I.U. C.G. per gram of acetone dried tissue (Table I).

Results

(1) *Semi-quantitative*

Figure 1 shows the results obtained by single semi-quantitative estimations from 632 pregnancies from the 3rd to the 40th week. It will be seen that urines from some pregnancies contain enough C.G. to produce a positive biological response in a dilution of 1 in 100 and sometimes in a dilution of 1 in 150. Urines positive in such dilutions may appear as early as the 5th or as late as the 14th week after the last menstrual period. The majority occur in the 3rd month when there is a temporary peak excretion of C.G. It will further be seen that with the exception of the 1st month of pregnancy, positive results in a dilution of 1 in 10 are obtained right up to term, indicating that post-peak values of 30,000 I.U. C.G. per litre are not exceptional.

When the excretion of C.G. from 67 patients before the removal of the mole, and obtained between the 5th and 35th week of gestation, is compared, it is found that most of them fall within the range of values obtained from normal pregnancies. The distribution of these cases of pregnancy and mole which are positive in a dilution of 1 in 100 or more is shown in Figure 2.

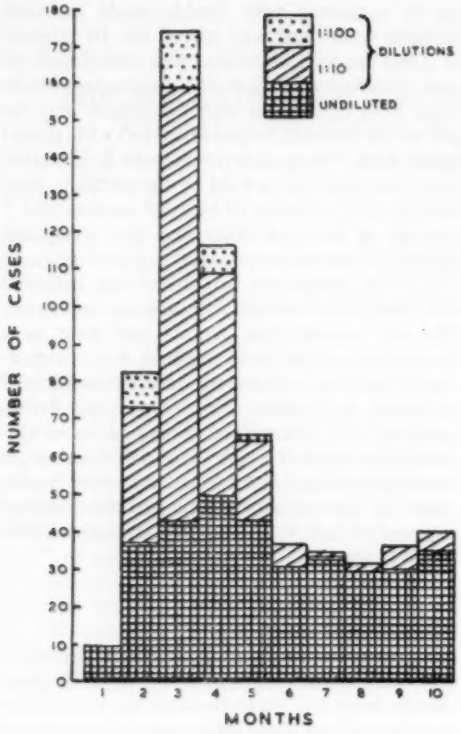

FIG. 1

The excretion of C.G. in 632 cases of normal pregnancy as estimated by the dilution test.

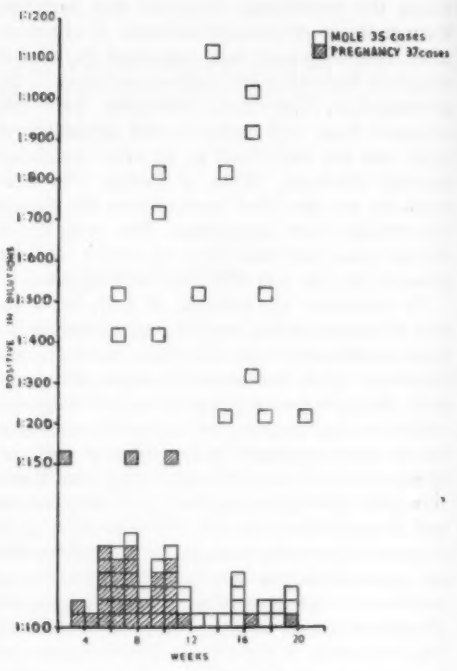

FIG. 2

C.G. excretion in 37 pregnancies and 35 cases of hydatidiform mole which were positive in dilutions of 1 in 100 or more.

In only 3 pregnancies was a result positive in a dilution of 1 in 150. With 2 exceptions urines collected after the 12th week of pregnancy were positive only in a dilution of 1 in 10. The exceptions were urines from 2 multiple pregnancies giving a positive response in dilutions of 1 in 100 in the 17th and 20th weeks. Figures 3 and 4 illustrate, in the immediate post-partum period, the use of dilution tests in estimating C.G. levels in urine. The excretion pattern as exemplified by those patients in Figure 3 is typical of the uncomplicated case. The urines from 43 patients were negative within 1 month after the removal of the mole. The earliest date at which a test was found to be negative was 2 days after removal of the mole. It was impossible to estimate how soon these patients stopped excreting C.G. as urines were sent in at varying times after the evacuation of the mole.

In those patients where some chorionic tissue is retained, there is a continued excretion of gonadotrophin until the tissue is removed or regresses spontaneously. Figure 4 depicts urinary C.G. levels after incomplete removal of the mole. These patients excreted C.G. for a considerable time, and in Case 83 temporary negative phases occurred twice. This emphasizes the need for doing more than one follow up test because a single negative result may be misleading.

When the C.G. titre falls below 3,000 I.U. per litre, and it is necessary to know the concentration in the urine, bio-assays are done. Figure 5

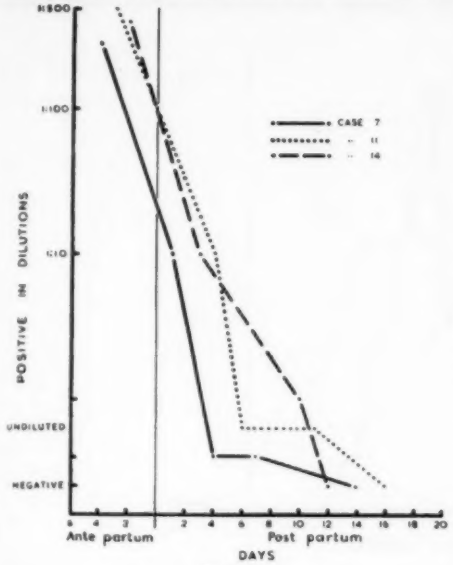

FIG. 3

The excretion of C.G. before and after complete removal of hydatidiform mole.

shows results obtained in this way; Hogben tests were also done on each specimen. With the exception of urine collected on day 71, which contained 2,850 I.U. C.G. per litre, all specimens were negative.

(2) *Quantitative*

Quantitative estimations were done on 88 urines from 7 patients with a history of hydatidiform mole, and 10 urines from 2 pregnancies. Approximate values were first determined from the results given by dilution tests and the final values obtained with groups of male Xenopus. Specimens from each case were collected at intervals of not more than 3 days and the cases were followed until the amount of C.G. fell below 300 I.U. per litre of urine. The results of these assays are shown in Figure 6.

Removal of the mole or placenta results in a sudden fall in the urinary level of C.G., all cases having a similar post-partum excretion pattern. Negative Hogben tests (<3,000 I.U./litre) were obtained with the urines of all cases by the 10th day post-partum, and, with the exception of Case 1, remained so. Case 1 is of particular

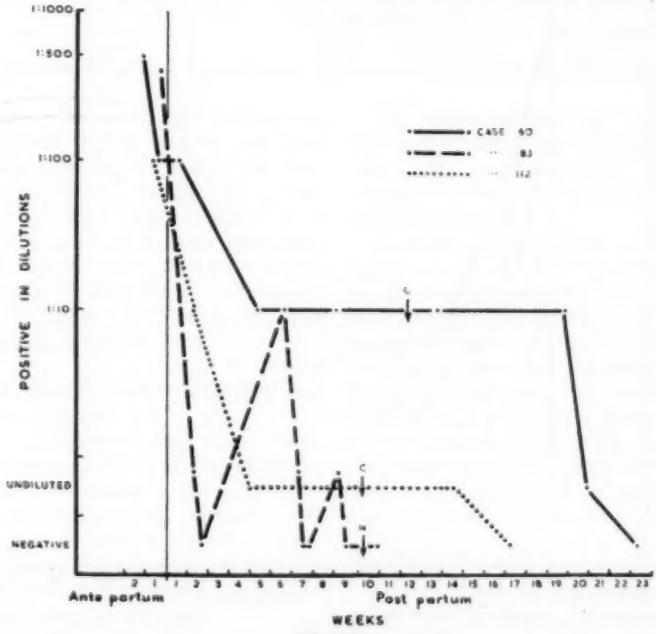

FIG. 4

The excretion of C.G. in 3 cases where removal of mole was incomplete. (C. Curettage, H. Hysterectomy.)

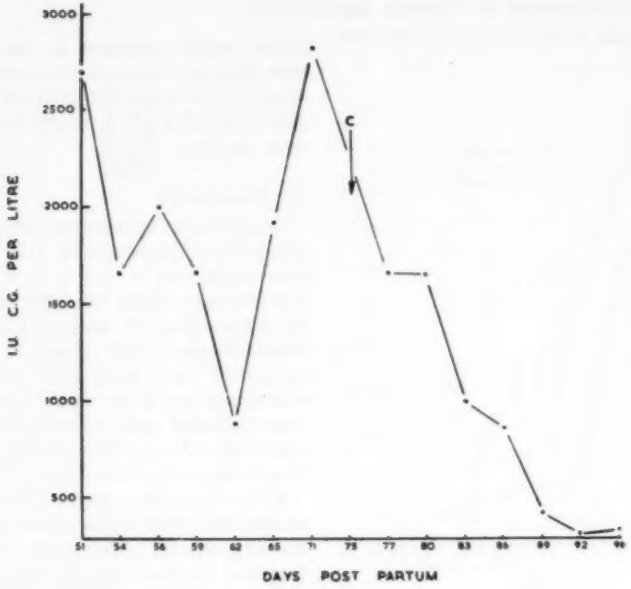

FIG. 5

Quantitative estimation of C.G. in a patient with retained chorionic tissue.

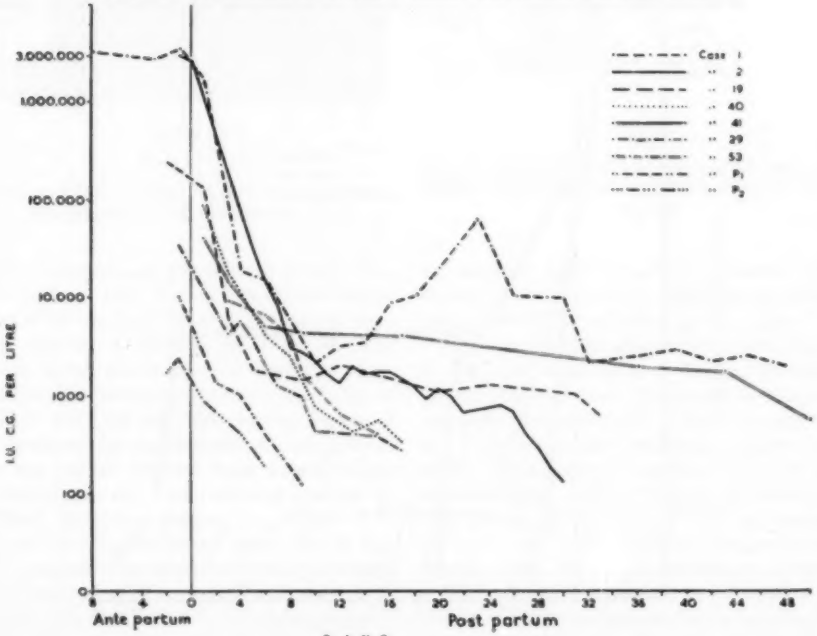

FIG. 6

Ante- and post-partum quantitative estimations of C.G. in 7 patients with hydatidiform moles and 2 cases of normal pregnancy.

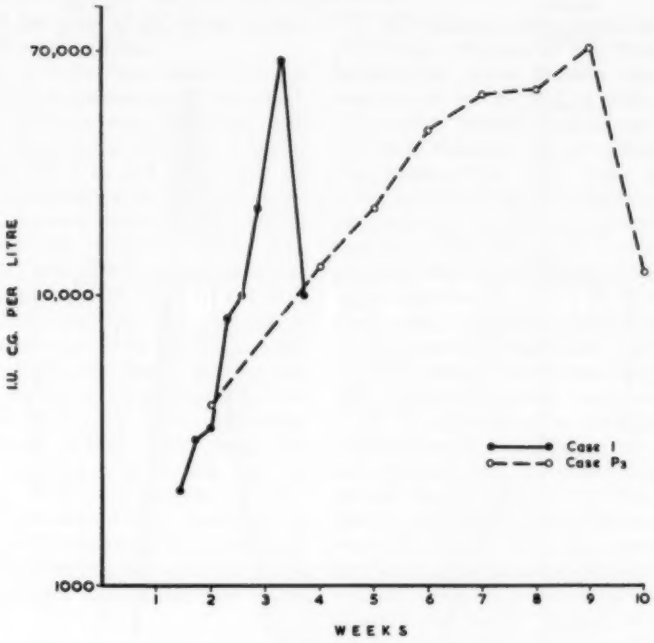

FIG. 7

The rise of excretion during normal pregnancy and a typical hydatidiform mole.

interest because a 2nd mole, the presence of which was detected by the dilution test, was obtained 24 days after the removal of the first. Excretion of C.G. during the growth of this mole is shown in detail (Fig. 7) where it is compared with a case of normal pregnancy (P3). The C.G. titre in Case 1 rose from 2,125–65,000 I.U./litre in 13 days before its removal, and from 4,170–72,000 I.U./litre in 48 days during pregnancy.

(3) *Comparison between Semi-quantitative and Quantitative Methods*

Quantitative estimations are done when precise information about the excretion of biologically active substances is required. They are, however, time consuming, expensive, and require the keeping of large stocks of animals. When all that is required is a knowledge of the increase or decrease in the excretion of C.G., semi-quantitative tests are adequate.

The following example shows the results obtained by converting "dilutions" into absolute units and comparing them with the results obtained by bio-assay on an aliquot of the same specimen (Fig. 8).

A closer approximation to the quantitative values can be obtained by narrowing the range of dilutions employed. The curve of C.G. excretion obtained by both methods is similar, and, with the exception of 1 result, quantitative estimations fall within the range of values given by the dilution tests. The anomaly is due to a weak positive result being given by the Hogben test with an undiluted urine, suggesting a concentration of approximately 3,000 I.U. per litre. The amount of C.G. in this particular specimen was 2,125$\pm$400 I.U. per litre.

(4) *Tissue Extracts*

Table I shows the concentration of C.G. in moles and placentae. Results of assays are

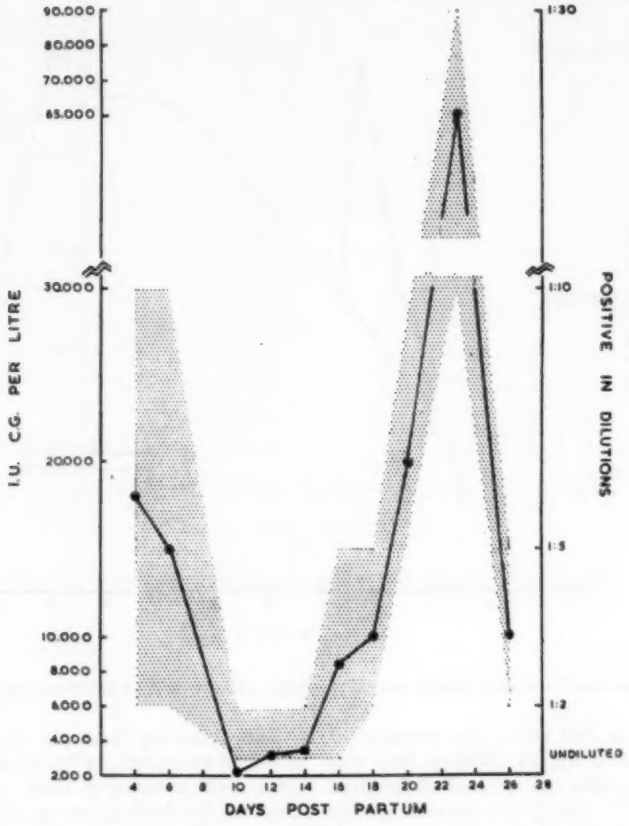

FIG. 8

Comparison between semi-quantitative and quantitative methods of estimating C.G.

TABLE I

C.G. Concentration per Gram of Tissue in 2 Normal Placentae and 7 Hydatidiform Moles
(Figures in parentheses refer to day on which estimations were made)

Case	Tissue	Gestation	I.U. C.G. Per Gram	I.U. C.G. per Litre of Urine	
				Ante-partum	Post-partum
205	Mole	24 weeks	32,100	600,090 (12)	5,700 (7)
29	Mole	15 weeks	20,034	34,000 (1)	4,160 (3)
40	Mole	24 weeks	14,300		87,500 (1)
3	Mole	11 weeks	3,750		30,000 (3)
41	Mole	23 weeks	2,710		40,000 (1)
2	Mole	17 weeks	2,452	3,000,000 (1)	2,550,000 (1)
6	Mole	18 weeks	1,550		9,050 (4)
P2	Placenta	Term	136	2,350 (1)	875 (1)
P1	Placenta	Term	106	10,000 (1)	1,364 (2)

expressed in I.U. per gram of dry tissue as only part of the mole was available.

There is from 14 to 300 times more C.G. per gram of tissue in the moles than in the placentae. However, the 2 placentae were "full-time" and are not strictly comparable with the 7 moles obtained between the 11th and 24th weeks of gestation. The concentration of C.G. per gram wet weight of placental tissue remains fairly constant from the 20th week until term. Concentrations during the second month of pregnancy are, approximately 100 times greater than those found at term (Diczfalusy, 1953). Although ante- and post-partum levels of C.G. were estimated, there is little correlation between the amount of C.G. per gram and per litre. This was expected, because if there is a direct relationship between the amount of C.G. in the tissue and that found in the urine, then it will only be discovered when moles are assayed in their entirety and the amount of C.G. contained in them compared with that circulating in the blood and the amount excreted during a period of not less than 24 hours prior to the evacuation of the mole.

Discussion

The results obtained show that a single dilution test as a means of distinguishing between a normal pregnancy and a mole is of little value. It has been suggested that positive reactions from highly diluted urines obtained after the peak excretion of gonadotrophin in normal pregnancy might be more reliable (Hobson, 1954). Since then urines from 2 multiple pregnancies have given positive reactions in dilutions of 1 in 100; these tests were done in the 17th and 20th weeks of pregnancy. Hamburger (1944) has reported a single case of normal pregnancy in which 900,000 I.U. per litre was excreted. Values of the order of 450,000 I.U. C.G. per 24 hours are only occasionally reported (Smith, Albert and Randall, 1951). Urines from 3 cases described here were positive in dilutions of 1 in 150 but negative in 1 in 200, i.e., they contained between 450,000 and 600,000 I.U. C.G. per litre. It would seem therefore that a urine, particularly if collected after the 14th week of pregnancy, which gives a positive reaction in a dilution of 1 in 200 indicates the presence of a mole. Tests positive in a dilution of 1 in 10 are of no value because the urines from a small number of pregnancies are positive in such dilutions right up to term. Weakly positive and even negative biological reactions can be obtained with urine concentrates from mole cases. In the present series the urine from 3 patients with moles *in situ* gave repeated negative biological reactions. This may have been due to the fact that only small amounts of actively secreting tissue were present or possibly because the C.G. was in some way inactivated. A negative result does not exclude the presence of mole tissue, just as repeatedly negative results are occasionally encountered with perfectly normal pregnancies (Hobson, 1954). Caution must be exercised when interpreting the results of dilution tests. They provide information to be considered together with the clinical data. The impression that a urine which gives a positive result in dilutions of 1 in 100 or even 1 in 150 indicates the presence of a mole has led to the termination of several pregnancies. Dilution tests are most useful in detecting the presence of some retained tissue after the evacuation of the major part of the mole. We have found that it is not unusual for urines from post-molar cases to give positive responses even when there was no chorionic tissue in the curettings. Because of this some clinicians assumed that the test had given a "false positive" result. Complete evacuation of the tissue producing the gonadotrophin must result in a drop in the circulation and excretion of C.G. and prolonged excretion of C.G. can only be due to retained chorionic tissue. Negative biological tests are obtained within 7 to 96 hours after delivery of the placenta (Crew, 1936). The excretion of C.G. after its injection into non-pregnant women, normal males and males with hypogonadism ceases between 3½ to 7 days after injection (Lloyd, Hughes, Eva and Lobotsky, 1949; Leach, Tokuyama and Maddock, 1954). Really accurate information on the excretion of C.G. can only be obtained when tests are done, on a large series of patients, at intervals of not less than 3 days following the removal of the mole. This can only be achieved by the closest cooperation between the clinician and the laboratory.

This work has shown that every patient with a mole should have monthly tests for 6 months after evacuation of a mole. The continued excretion of C.G. in the absence of a new pregnancy means either a secondary growth or retained chorionic tissue. One in every 40 molar pregnancies is said to become a chorion-epithelioma compared with 1 in 160,000 pregnancies (Hertig, 1950). The regular use of dilution tests after the removal of a mole is advocated because in the majority of cases these tests will detect the presence of metastases before the condition is clinically evident. The results obtained about the excretion of C.G. in patients with chorionepithelioma are to be published.

Summary

(1) The C.G. concentration in urine was estimated by the Hogben dilution test and bio-assays using male Xenopus laevis.

(2) Data are presented on the ante- and post-partum excretion of C.G. in 105 patients with a hydatidiform mole. For comparison semi-quantitative estimations were made on urines from 632 pregnancies.

(3) When the mole is completely evacuated negative biological tests are to be expected within 1 month. Incomplete removal of the mole results in positive biological reactions until the retained chorionic tissue is removed or regresses spontaneously.

(4) Comparison is made between the semi-quantitative and quantitative methods for the estimation of C.G.

(5) The concentration of C.G. in 7 moles and 2 placentae was estimated.

The author wishes to thank those clinicians and practitioners who provided clinical information about patients and supplied specimens for this investigation.

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APPENDIX

Since this paper was sent to press the following observations were completed. Hobson (1952) has pointed out the difficulties of collecting data, over a period of time, about the excretion of C.G. with the mole *in situ*. In the present investigation, where the ante-partum excretion of C.G. in 67 patients was estimated, it was not possible to obtain more than 2 or 3 specimens of urine from each patient before the mole aborted or was removed. The following case is of particular interest because semi-quantitative estimations were made on 10 specimens of urine collected between the 17th and 22nd weeks after the L.M.P. and before the removal of the mole. These results are compared with those obtained from 2 normal pregnancies of the same duration (Fig. 9).

It has been made quite clear that estimations on a single specimen of urine are usually of little use in predicting the presence of a mole unless the test is positive in high dilutions (1 : 200 or more). In the case illustrated (Fig. 9) a confident diagnosis of hydatidiform mole was made by this laboratory as a result of the first specimen being positive in a dilution of 1 : 300. However, had the first test been positive with undiluted concentrate only, as was the second specimen, it might have been thought that this was a normal pregnancy. A third specimen collected 3 days later contained not less than 450,000 I.U. C.G.

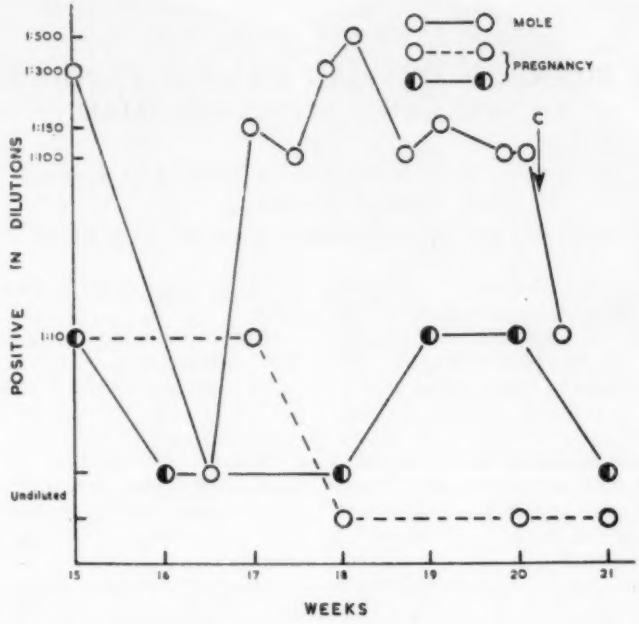

FIG. 9

Excretion of C.G. with mole *in situ*. Compared with 2 cases of normal pregnancy. (C. Curettage.)

per litre and with the exception of the urine obtained at 16½ weeks of pregnancy the amounts of C.G. excreted remained at a pathological level until the removal of the mole. After the expulsion of the mole daily estimations were done, and the first negative test was obtained 6 days post-partum; subsequent tests have remained negative.

This case is also interesting because bleeding first occurred during the 9th week of pregnancy, a time at which the allantois and trophoblast fuse to form the chorion. Ewart (1917) and Hertig (1950) have pointed out that this is the most common time at which pathological foetuses abort. The chorions of these defective foetuses show hydatid swelling and constitute the early phase of hydatidiform mole. In view of these observations it might be advisable to follow up carefully cases of pregnancy in which bleeding occurs at this time. Whilst the majority of such pregnancies will abort, or recover and go to term, those pregnancies which eventually become hydatidiform moles might be diagnosed earlier if dilution tests were used to detect the excretion of abnormally large amounts of C.G.

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ON A SINGULAR OVARIAN CHANGE PRODUCED BY METHYLANDROSTENEDIOL (MAD)

BY

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METHYLANDROSTENEDIOL (MAD) possesses rather unusual pharmacological actions. In the adrenal cortex of the rat it causes a deposition of numerous hyalin, PAS-positive droplets. This change is accompanied by hypertension, nephrosclerosis and cardiac lesions, similar to those normally elicited by overdosage with desoxycorticosterone acetate (DCA). However, MAD —unlike DCA—fails to produce any of these cardiovascular and renal lesions in the adrenalectomized animal maintained on NaCl or on small doses of corticoids. Hence, it was assumed that MAD acts by producing some derailment in the steroid-hormone metabolism of the adrenal cortex (Salgado and Selye, 1954a; 1954b; 1954c). It has also been shown that MAD interferes with the normal corticotrophic effect of exogenous A.C.T.H. (Selye and Bois, 1954).

In the course of various experiments it had been noticed, incidentally, that the ovaries of rats receiving large doses of MAD become intensely hyperaemic while the corpora lutea assume a singular and quite distinctive whitish colour. Even the most superficial histological examination of these ovaries revealed changes in their microscopical structure, such as we had never observed before, under any other experimental conditions. It has therefore been decided to undertake a systematic study of the ovarian lesions produced by MAD in normal rats, as well as in adrenalectomized animals maintained by various corticoids.

METHOD

Forty female Sprague-Dawley rats were subdivided into four groups of 10 animals each as outlined in our Table. The mean initial bodyweight was 160 g., in all four groups, with a maximum range of 10 g. above or below the mean.

MAD (17α-methyl-Δ^5-androstene-3β, 17β-diol) microcrystals were administered subcutaneously at the daily dose-level of 5 mg. in 0·2 ml. of water, "Tween 80" being used as a suspending agent.

*Cortisol** (400 μg/day) and *desoxycorticosterone* (100 μg/day) were both given in the form of microcrystals of their acetates, subcutaneously in 0·2 ml. of water, using the same suspending agent.

Adrenalectomies were performed through the dorsal route, under ether anaesthesia, on the same day on which treatment with the various steroids began. Ten days later the animals were killed with chloroform and their ovaries fixed in "Susa" solution for subsequent weighing and histological study.

RESULTS

The general plan of the experimental arrangement, as well as the ovarian weights (with their standard errors), are summarized in Table I.

The ovarian weight was only slightly decreased by MAD; however, even mere macroscopic inspection showed that the ovaries were very hyperaemic and the corpora lutea had a characteristic ivory-white colour.

Upon histological examination, it was found that, in all individuals of the three MAD-treated groups, the same type of ovarian lesion had

* In agreement with the suggestion made by Shoppee (1953), the term cortisol is used here in preference to "hydrocortisone", since it eliminates confusion with 4,5-dihydrocortisone and obviates the possible implication that "hydrocortisone" is to be regarded primarily as a mere derivative of cortisone.

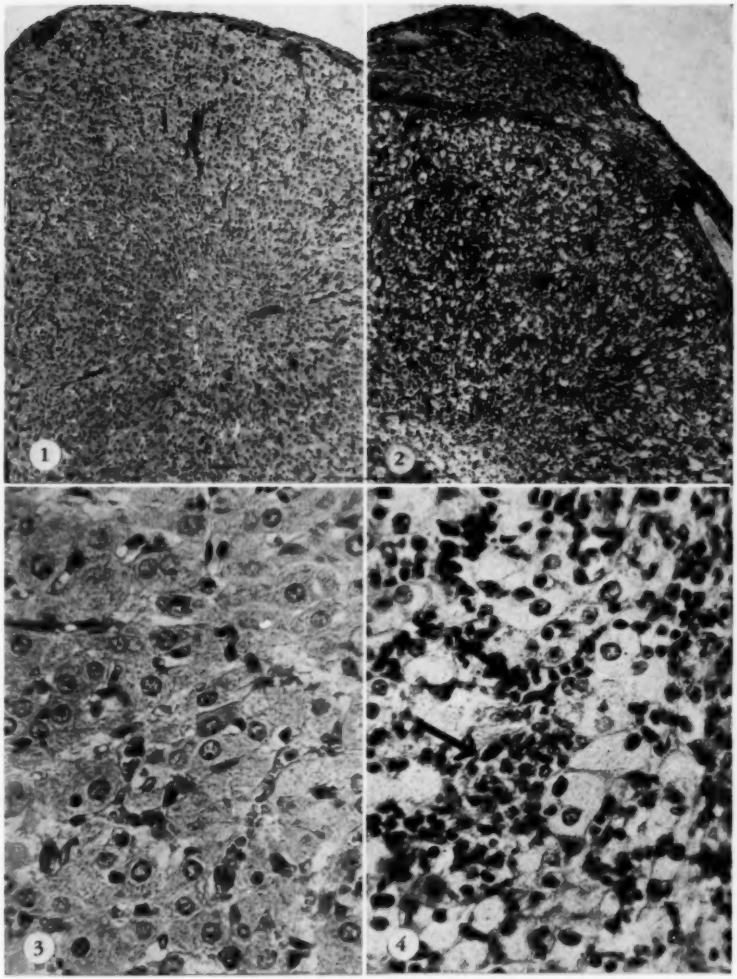

FIG. 1

General aspect of a normal corpus luteum from a rat of Group 1. ×75.

FIG. 2

General aspect of a corpus luteum in an MAD-treated normal rat of Group 2. Note the intense infiltration with small dark cells between which some enlarged very clear "foam-cells" are especially conspicuous. ×75.

FIG. 3

Region from the corpus luteum shown in Fig. 1 to illustrate normal aspect of individual corpus luteum cells at higher magnification. ×337.

FIG. 4

Region from the corpus luteum shown in Fig. 2. Note large "foam-cells" with comparatively dense nuclei and the infiltration of dark small cells between them. Note also numerous lymphoid and polymorphonuclear cells, both in the capillaries (upper arrow) and in the stroma between the foam-cells (lower arrow). ×337.

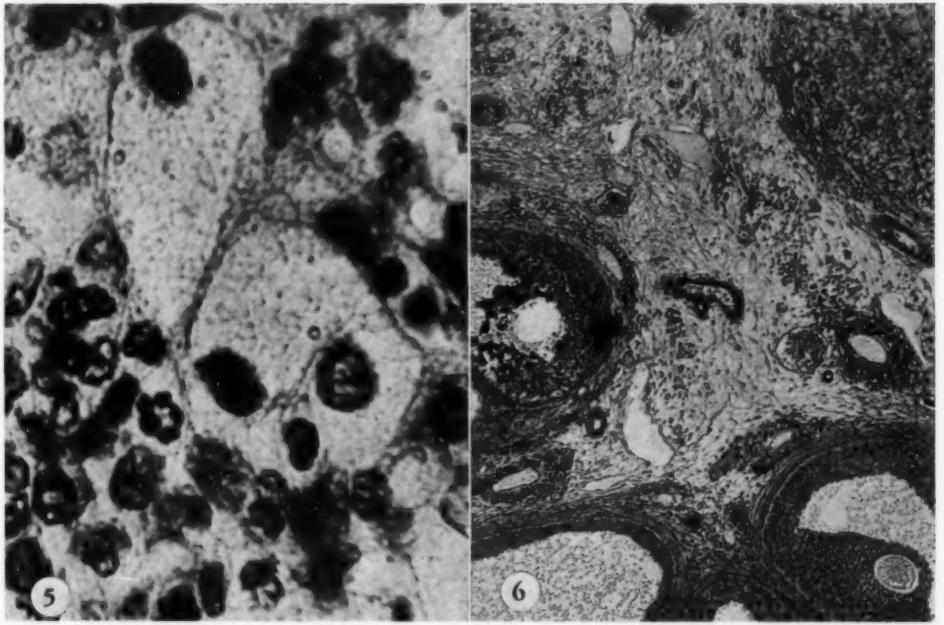

FIG. 5

Detail from the central field of Fig. 4. "Foam-cells" with their dense eccentric nuclei as well as the lymphoid and polymorphonuclear cells are visible. ×1000.

FIG. 6

Region from the medullary portion of the ovary in an MAD-treated normal rat of Group 2. Note the hyperaemia and oedema of the stroma, the great atrophy of the interstitial cells (distinguishable only as small dark dots within the oedema of this connective tissue) and the typical infiltration of a corpus luteum (part of which shows in the upper-right corner of the field) are all clearly visible. The granulosa of the follicles in the lower part of the field is unchanged. ×100.

TABLE I

Effect of MAD upon Ovarian Weight in Intact and in Adrenalectomized (Corticoid-treated) Rats

Group	Treatment	Ovaries
I	Normal, Untreated	47·4±3·4
II	Normal, MAD	38·2±2·2
III	Adrenalectomized, Cortisol, MAD	39·2±4·9
IV	Adrenalectomized, Cortisol, DCA, MAD	37·5±2·6

developed. These appeared to be least severe in the intact (Group II) and most pronounced in the adrenalectomized animals receiving both cortisol and DCA (Group IV), but individual variation was quite marked, within any one group. Since, furthermore, these morphological changes do not lend themselves to statistical evaluation, this apparent difference in the severity of the lesions may be coincidental.

Histologically, the typical lesion is primarily characterized by an extremely pronounced dilatation of the ovarian veins. This is manifest in the medullary portion of the gland, where the large sinuses are situated, but also in the stroma, the theca nests and the corpora lutea, which contain smaller veins. Recently developed cystic corpora lutea (which have not yet accumulated many lipid droplets) are much less markedly affected by this venous stasis than the fully developed, or involuting, older corpora lutea. Occasionally, extremely dilated sinuses are also seen underneath the ovarian capsule, on the surface of large corpora lutea. Indeed, these may become wide enough to be clearly visible to the naked eye.

The theca-cell nests ("interstitial gland") within the ovarian stroma also show another characteristic change, namely, a pronounced involution of the epithelioid cells, with a nuclear rearrangement, in such a manner that the clear spaces between the basophilic chromatin assume the appearance of the spokes of a wheel. Similar cells have been observed in the ovaries of hypophysectomized rats and were given the name "wheel cells". They are somewhat reminiscent of plasma cells and usually occur as a result of LH deficiency (Selye, Collip and Thomson, 1933). In some animals the stroma between the theca-cell nests became extremely oedematous.

The most typical changes occur, however, in the parenchymatous elements of the corpora lutea themselves. Here, the entire tissue appears to be transformed into a structure which is singularly reminiscent of the xanthomatoses, for instance, of Niemann-Pick's disease. Some of the corpus luteum elements retain many of their original characteristics, but become somewhat enlarged and laden with light vacuoles, so that they assume the appearance of "foam-cells". On frozen sections stained with Sudan III, these vacuoles stain a bright red; they presumably contain lipid materials. Between the foam-cells, there is an infiltration of much smaller, rather irregular elements, containing little or no lipid. At certain places, they resemble lymphocytes, monocytes or histiocytes, but occasionally there are typical polynuclear leucocytes among them. This picture of large lipid-storing cells, between strands of small lymphoid or haemopoietic-tissue-like elements, also bears a striking resemblance with the changes in the adrenal cortex which we had observed in tumour-bearing rats and in animals given chronic treatment with large doses of STH (Selye, 1950). Sections stained with the McManus technique (McManus, 1948) revealed no PAS-tingible granules, comparable to those seen in the adrenals of MAD-treated rats (cf. Figs. 1–6).

The uteri and the preputial glands of all the MAD-treated animals were markedly enlarged and there was also some mammary-gland proliferation. However, from the appearance of these organs we cannot draw any definite conclusions as to possible hormonal derangements resulting from this action of MAD upon the ovary.

In the present communication we merely wanted to point out that MAD, which had been shown to cause a marked derangement in the histological structure and steroid metabolism of the adrenal, also produces a rather characteristic morphological change in the ovaries. We had not seen any comparable lesions previously in rats treated with a variety of related steroids, such as testosterone, androsterone, methyltestosterone, etc. Chronic treatment with testosterone propionate can cause ovarian atrophy (Selye, 1940a; 1940b; 1941a; 1941b), as well as the formation of large corpora lutea and follicle cysts (Selye

of the field is unchanged. ×100.

and Friedman, 1940), but these changes are qualitatively different from those produced by MAD.

Summary

In albino rats, overdosage with methyl-androstenediol (MAD) produces a singular and rather characteristic ovarian change not previously observed to occur after treatment with pharmacologically and chemically related steroids. There is marked venous hyperaemia in the ovarian stroma, in the theca nests and in the corpora lutea. The microscopical appearance of the corpora lutea is also changed by the development of numerous large lipid-storing "foam-cells", between which there is a dense infiltration with darker elements, resembling monocytes, lymphocytes and sometimes polymorphonuclear leucocytes.

Previous work had shown that MAD produces quite characteristic changes in the adrenal cortex, with the accumulation of PAS-positive droplets. These are accompanied by renal and cardiovascular lesions, which are prevented by adrenalectomy. On the other hand, the above-mentioned ovarian changes are not influenced by removal of the adrenals, even in rats kept in good condition by maintenance doses of corticoids.

Acknowledgments

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THE RESULTS OF RADIUM TREATMENT OF CANCER OF THE UTERINE CERVIX WITH SPECIAL REFERENCE TO GLANDULAR AND STUMP CANCERS

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ALTHOUGH irradiation will probably continue to be the mainstay of treatment for the majority of women suffering from cancer of the uterine cervix, blood transfusion and modern anaesthesia have combined to bring surgical treatment again to the forefront of discussion. With radiotherapy, 2 out of every 5 women, even when seen relatively early, will succumb to the disease within 5 years, and it is still not clear, at least as far as epithelioma is concerned, to what extent surgery or a combination of surgery and irradiation will improve these results.

It is no easy matter to compare the results of radium and operation, and this paper does not attempt to do so. The issue is whether better results are possible on the one hand by operating on a proportion of the cases and irradiating the remainder or, on the other hand, by irradiating all cases, but the difficulty is to obtain figures that are strictly comparable. Hospital results are recorded fairly uniformly as "stage rates" and "absolute recovery rates"—the latter being the proportion of apparently recovered patients expressed as a percentage of the total number *seen* at the institution with a view to treatment, but both "stage rates" and "absolute recovery rates" as applied to hospital material, have their inherent defects. Clinical stage grouping is subject to considerable personal variation and the "absolute recovery rates" usually refer to cases seen at one hospital, which may or may not be representative of the disease in the community. Hospital figures reveal considerable differences in the quality of the clinical material seen at one institution as compared with another, and in view of these differences Heyman and Segerdhal (1952) refer to hospital figures as "biased absolute recovery rates". They suggest that the term "absolute recovery rate" be reserved for the proportion of apparently recovered patients expressed as a percentage of the total number of cases within a *geographically defined area*, and the main reason for placing the Cardiff figures on record is that they would appear to approach this desideratum. During the period under review, Cardiff Royal Infirmary was the only centre in this area undertaking the treatment of cervical malignancy. In 1930 a modified Stockholm Technique of radium therapy was adopted and employed routinely until 1948 (Maliphant, 1947). During this period 1,116 patients were seen with a view to treatment, of whom 1,094 were treated, the remaining 22 patients or 2 per cent being rejected on account of advanced disease.

The cases were grouped originally into the four clinical stages recommended by the Radiological Sub-Commission of the League of Nations (1929), and microscopic confirmation of the diagnosis was routine. Supplementary X-irradiation was not employed, and neither was radical surgery during the period under review.

Follow-up was not easy with the general movement of population, particularly during the war years, and 6 per cent of the patients were lost to follow-up within 5 years of treatment. These cases, in addition to those dying of incidental disease during the first 5 years, are included as "deaths from cancer". The results, assessed in terms of 5-year survival, are shown in Table I.

The 5-year salvage was 28 per cent of all cases seen; 61 per cent of Stage 1, 40 per cent of Stage 2, 18 per cent of Stage 3, and 4·8 per cent of Stage 4.

Since 1939 the revised League of Nations Classification (1937) has been used and, among other modifications, clinical Stages 2 and 3 were subsequently broken down into sub-groups. The results in Table II show considerable differences within each stage according to the mode of extension. In Stage 2 cases with only parametrial involvement the 5-year survival rate was 49 per cent, with only vaginal involvement 43 per cent, and in cases with both parametrial and vaginal involvement 34 per cent. During this period (1939–1948) there was a substantial increase in the proportion of cases seeking treatment in the second clinical stage of cancer, with a corresponding improvement in the overall 5-year survival rates, both relative (31 per cent) and absolute (30 per cent).

Late Results

The 10-year results (Table III) relate to 764 patients treated between 1930 and 1943, a group heavily weighted with advanced disease. Sixty-three per cent of these cases were in the 3rd or 4th stages of cancer and the 5-year survival rate was only 27 per cent.

Of the 204 women who survived 5 years, 71 per cent are known to have survived 10 or more years. Sixteen per cent died of cancer during the second quinquennium, 4 per cent succumbed to

Table I

Radium Treatment of Cancer of Uterine Cervix, 1930–1948

Stage	Number of Patients Seen	Treated	Alive after 5 years Number	Per cent Relative	Per cent Absolute
1	80 (7·1 per cent)	80	49	61	61
2	419 (37·5 per cent)	419	168	40	40
3	513 (46 per cent)	513	92	18	18
4	104 (9·4 per cent)	82	5	6	4·8
	1,116 (100 per cent)	1,094	314	28·7	28

22 patients (2 per cent) rejected on account of advanced disease.
71 patients (6 per cent) lost sight of during first 5 years.

Table II

Radium Treatment in Cancer of Uterine Cervix, 1939–1948
(Percentages in brackets)

Stage		Number Treated		Alive after 5 years	
1			44 (7)		25 (57)
2	Parametrial	126		62 (49)	
	Vaginal	44		19 (43)	
	Parametrial and Vaginal ..	148		50 (34)	
	Corpus	4		2	
			322 (51)		133 (41)
3	Parametrial	204		36 (17)	
	Vaginal	20		3 (15)	
	Parametrial and Vaginal ..	29		0	
			253 (40)		39 (15)
4			13 (2)		1 (7)
			632 (100)		198 (31)
				Absolute	(30)

incidental disease and 9 per cent were lost to follow-up. After 10 years survival rates have little significance as they are so liable to be distorted by the natural death rate of an ageing population, but it is noteworthy that 10-year survival after radiotherapy is by no means synonymous with cure. Four of our patients were apparently well for periods ranging from 11 to 19 years and yet succumbed to cancer, the site of recurrence being in the lungs (11 years), iliac lymph glands (13 years), bladder (15 years) and liver (19 years). Similarity in histological pattern with the original tumour would suggest that these were long-delayed recurrences rather than fresh independent cancers.

Although the 5-year survival figures are accepted as the general standard of comparison, the survival rate curve falls steadily from the 3rd year onwards, so if it be deemed desirable to evaluate a particular modification in treatment before 5 years elapse, the 3-year figures serve as a reliable guide. As previously indicated, 15 per cent deducted from the 3-year survival figure provides a useful index to the probable 5-year end result (Maliphant, 1947).

Adenocarcinoma

Eighty-two or 5 per cent of the cases were primary glandular cancers of the cervix and they differed from epitheliomata in their clinical features and in their response to radium.

The youngest patient was 21 years and the oldest 77 years, but their average age was greater than that of women with squamous cell cervical cancers, approaching that of cancer of the corpus. This is evident when the incidence of adenocarcinoma is examined in the various age groups (Table IV)—rising from 2·8 per cent in the younger women, through 5 per cent in the intermediate age group (45 to 64 years) to 8 per cent in the older women.

The fertility of women with adenocarcinoma of the cervix is shown in Table V. While 37 per

Table III

Radium Treatment in Cancer of Uterine Cervix, 1930–1943
(Percentages in brackets)

Stage	Number Treated	Alive after 5 years	Five to Ten Years			Alive after 10 years
			Died of Cancer	Died of Incidental Disease	Untraced	
1	51	35 (70)	6	0	2	27 (53)
2	230	86 (37)	15	6	7	58 (25)
3	404	79 (19·5)	13	2	8	56 (14)
4	79	4 (5)	0	0	1	3 (3·8)
	764	204 (27)	34 (16)	8 (4)	18 (9)	144 (19)

Table IV

Adenocarcinoma of Uterine Cervix—Incidence
(Percentages in brackets)

Age Group	No. of Cases of Cancer of Cervix	Epithelioma	Adenocarcinoma
20–44 years	457 (28·3)	444	13 (2·8)
45–64 years	973 (60·1)	919	54 (5·5)
65– years	188 (11·6)	173	15 (8)
	1,618 (100)	1,536	82 (5)

TABLE V

Adenocarcinoma of Cervix—Childbearing
(In Women of Completed Fertility only, Aged 40 and Over)

Number of Children	Adenocarcinoma of Cervix		Family Census Cardiff, 1946 Per cent		Epithelioma of Cervix Per cent	
0	8 (10 per cent)		14·5		5·1	
1 or 2	30 (40 per cent)		36·2		32	
		50 per cent		50·7		37·1
3 and over	38	50 per cent		49·3		62·9
	76					

cent of the women who developed epithelioma of the cervix were either childless or had few children, the corresponding figure for adenocarcinoma was 50 per cent, which is approximately that of the community (Table V). Unlike epithelioma, adenocarcinoma of the cervix does not seem to be so intimately related to childbearing. It is just as liable to develop in the "unused uterus" as in the parous uterus, its fertility pattern being intermediate between that of squamous cell cancer of the cervix and adenocarcinoma of the corpus.

Its growth properties and mode of extension resemble those of epithelioma, but it more often presents as a hypertrophic growth, frequently with cauliflower-like proliferation (Table VI). Adenocarcinomata are also well represented in the group of cervical cancers which adopt an endocervical mode of spread. The response of the glandular cancers of the cervix to radium treatment has been poor, and only 22 per cent of those patients seen in the first and second clinical stages of the disease survived 5 years, only half the survival figure for a corresponding group of epitheliomata.

TABLE VI

Adenocarcinoma of Cervix—Macroscopic Types
(Percentages in brackets)

	Adenocarcinoma of Cervix	Epithelioma of Cervix
Hypertrophic ..	37 (45)	213 (28)
Ulcer	19 (23)	434 (57)
Endocervical ..	19 (23)	68 (9)
Nodular, etc. ..	7	47
	82	762

CANCER OF THE CERVICAL STUMP

There were only 23 stump cancers in our series, an incidence of 1·4 per cent. Seventeen or 74 per cent were over 50 years of age, compared with 53 per cent of our cases of cervical

TABLE VII

Adenocarcinoma of Cervix—Results of Radium Treatment, 1930–1948

Stage	Adenocarcinomata Number Treated	Adenocarcinomata Alive after 5 years		Epitheliomata Number Treated	Epitheliomata Alive after 5 years	
1	3	2		77	47 (61 per cent)	
2	28	5		391	163 (41·7 per cent)	
	—	—	22 per cent	—		45 per cent
3	26	4		487	88 (18 per cent)	
4	1	0		81	5 (6 per cent)	
	—	—	15 per cent	—		16·4 per cent
	58	11	19 per cent	1,036	303 (29·1 per cent)	

cancer in general. There was also a slightly greater incidence of nulliparous women (Table VIII), but this was not as high as in most published series.

TABLE VIII

Carcinoma of Cervical Stump

Incidence: 23 (1·4 per cent) of 1,618 cases. All epitheliomata.

Age incidence: 17 (74 per cent) were over 50 years of age (cf. 53 per cent of our cases in general).

Parity: 2 were nulliparous (one of whom was unmarried) (9 per cent cf. 5 per cent).

Interval since hysterectomy ranged from 3 to 34 years.

Results of Radium Treatment, 1930–1948

Stage	No. treated	5-year survival
1	1	0
2	13	7
3	7	0
4	0	0
	21	7

1 patient developed a vesico-vaginal fistula.
3 are living, 23, 12 and 8 years since treatment.
1 died of incidental disease after 11 years.

Women with stump cancer are generally a little older and have a higher incidence of nulliparity than cases of cervical cancer in general because of the selected fraction of the population from which they are drawn. The "stump population", women who have previously been submitted to supravaginal hysterectomy, are usually older and many are nulliparous, and these features are inevitably reflected in any series of stump cancers.

The interval since hysterectomy ranged from 3 to 34 years. Although the recognition of a long intra-epithelial phase has changed our conception of the natural history of cervical malignancy, we have adhered to the usual custom of accepting an interval of 3 years as indicative of a true stump cancer.

Women with cancer of the residual cervix seem to be more conscious of the significance of vaginal bleeding, and when compared with cases of cancer of the cervix in general, a relatively greater proportion of stump cancers were seen during the first and second clinical stages of the disease (Table VIII).

It has been suggested that, in view of the risk of urinary fistulae, stump cancers are best treated surgically. One of our cases developed a vesico-vaginal fistula, but the results of radium treatment have not been unsatisfactory (Table VIII). More than half the women seen in Stage 2 were alive after 5 years and 2 are still alive 23 years after initial treatment.

This survey would not have been possible without the cooperation of my departmental colleagues, and I am also indebted to Dr. Lewis-Faning for his advice and assurance that the deductions in the section on adenocarcinoma pass the relevant tests of statistical significance.

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A CHORION-EPITHELIOMA OF THE UTERUS IN A POST-MENOPAUSAL WOMAN

BY

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CHORION-EPITHELIOMA is a rare tumour with peculiar features which distinguish it from all other tumours. These features are of great interest in the study of malignant disease. For this reason cases are frequently reported in detail. Despite detailed reports and numerous extensive reviews there has been no adequate explanation of the bizarre features of this growth (Brews, 1939; Park and Lees, 1950).

Chorion-epithelioma is usually described as a tumour of one individual infiltrating the tissues of another. This description is only applicable to the type of growth which arises from the trophoblast of the developing embryo. It is not applicable to those growths which originate in the ovary or testicle or in teratomatous tumours at other sites.

Chorion-epitheliomata arising in teratoma or as a result of pregnancy are similar histologically. Attempts have been made in the past to call those arising from teratomata "chorion-epithelioma-like" tumours. The production of great quantities of gonadotrophin by some of the tumours supports the view that they are truly chorionic.

THE SITES OF CHORION-EPITHELIOMA

(a) *Originating in pregnancy*

Where it has had its origin in a pregnancy the chorion-epithelioma may occur at any of the sites at which an ovum may become embedded and growths have been recorded in the cervix, Fallopian tubes, pelvic cavity and ovaries as well as the body of the uterus. Where a growth associated with a pregnancy is found in a site remote from that of implantation of the ovum, e.g., the lungs, two explanations are offered.

The growth may be a secondary tumour, the primary having disappeared. As it is an accepted fact that both primary and secondary chorion-epitheliomata may regress this is quite a reasonable explanation.

The second explanation is that a chorion-epithelioma may arise at the site of implantation of chorionic villi which have been carried by the blood stream as emboli and deposited in the lungs or other organs.

(b) *Arising in teratomata*

These tumours are naturally found in the sites at which teratomata are found. These in order of frequency are the ovaries, the testes, the retroperitoneal region, the anterior mediastinum, the pre-sacral and coccygeal region and the base of the skull. Rarer sites include the pineal gland, brain and neck. Teratomata of viscera other than the gonads are extremely rare, e.g., the stomach (Large *et al.*, 1952) or the kidney (McCurdy, 1934).

When these two large groups of cases are excluded there remain a few cases of chorion-epithelioma which are not apparently associated with pregnancy or with a teratoma. In some cases the last known pregnancy was several years previously. There usually remains the possibility in these cases that there may have been a more recent and unrecognized pregnancy.

In a careful review of the literature, Park and Lees (1950) accept 3 cases which were not at the site of a teratoma or associated with a pregnancy. One of these was in a virgin aged 71 years reported by Maizels (1940). The other 2 were in men.

The case to be described here is a similar bizarre case in a post-menopausal woman.

FIG. 2
Uterus and appendages showing the large chorion-epithelioma at the fundus.

FIG. 1
X-ray of chest showing multiple secondaries in the lungs.

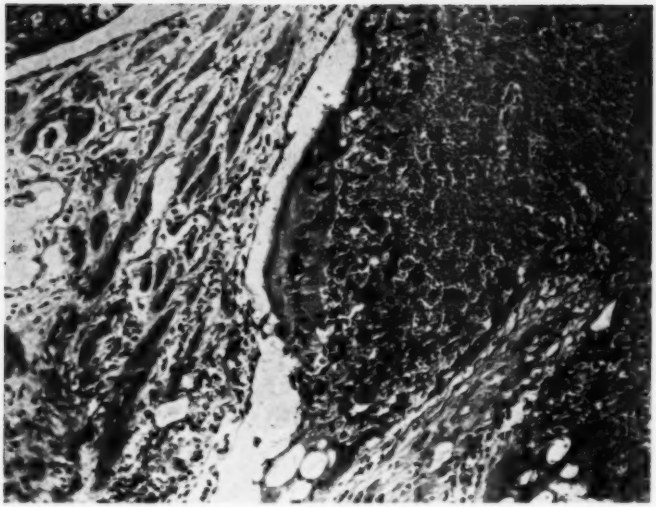

FIG. 3

A section of the myometrium showing necrosis of muscle cells and leucocytic infiltration associated with an intravascular metastasis. Haematoxylin and eosin. ×150.

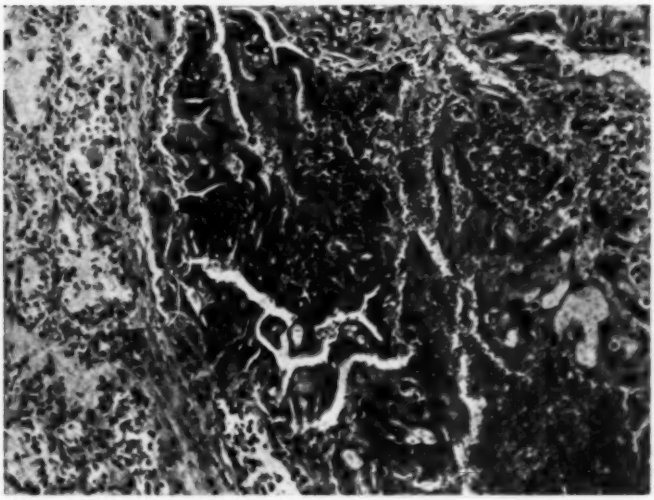

FIG. 4

Metastasis in the thyroid gland showing both Langhans' cells and the syncytial layer of the trophoblast. Haematoxylin and eosin. ×150.

Mrs. R.H., aged 59 years, was first seen at the Mayday Hospital, Croydon, on 15th January, 1954. She complained of heavy vaginal bleeding of 5-weeks duration.

Menstrual and Reproductive History. She had borne 8 children, their ages ranging from 39 years to 19 years. The last child was born when she was in her 40th year. She never had an abortion. Following the birth of her last child her periods had been regular until the age of 55 years when she had uterine haemorrhage. It was not possible to discover the exact method of onset of this haemorrhage but it seemed to have started as a normal period which went on for several weeks. In August, 1950, she was sent to Exeter radiotherapy centre from her home in Cornwall. A diagnosis of menopausal menorrhagia of non-malignant origin was made and she was treated by X-rays. On the 21st August she received two treatments (400 r) to anterior and posterior pelvic fields, the estimated dose at the centre of the pelvis being 350 r. No biopsy or examination under anaesthesia was performed at that time.

Following this treatment she returned home. She remained in good health and there was no further vaginal bleeding until the present episode 3 years and 4 months later.

The patient was a healthy looking country woman of short stature. There were signs of healed rickets in her skeletal system. No abnormality was detected in her cardiovascular system. Her blood pressure was 165/80 mm. of mercury.

There was a tumour the size of a 14-weeks pregnancy in the lower abdomen behind the symphysis pubis. There were no enlarged lymphatic glands palpable.

A uterine haemorrhage was in progress. The vulva, vagina and cervix were healthy. On bimanual examination the uterus was the size of a 14-weeks pregnancy. It was mobile and anteverted in position. The appendages were normal.

Operation. One week later the patient was admitted to hospital. Bleeding had continued since she was first seen. Her haemoglobin was 82 per cent. Examination under anaesthesia confirmed the previous findings. A diagnostic curettage produced thick curettings. A clinical diagnosis of carcinoma of the body of the uterus was made. The external os was closed with catgut sutures and an extended total hysterectomy and bilateral salpingo-oöphorectomy were carried out. This involved wide excision of the broad ligaments and parametrium with removal of a one-inch cuff of vagina. A Wertheim's clamp was used on the vagina as owing to its width two right angle forceps would not completely close it. During the operation 540 ml. of blood was given by intravenous drip.

Convalescence was uneventful except for some retention of urine which was treated by daily catheterization. A vaginal examination on 22nd February, 1954, 4 weeks after operation, showed that the vaginal vault was well healed. There was no sign of a secondary deposit in the vagina, vulva or pelvis. It was arranged that the patient would go to a convalescent home for 2 weeks prior to admission to the Chelsea Hospital for Women for irradiation therapy. The nature of the malignant tumour was not known at this time. On return from the convalescent home 2 weeks later it was found that she had become much thinner. She looked ill and had lost her appetite. Her only complaint was of urinary frequency. On examination she was found to have retention of urine with overflow. There were 2 secondary growths in the vagina. There was a small one at the vault of the vagina on the right side. The other was in the lower half of the vagina on the anterior wall and extended into both labia majora. There was no evidence of secondary deposits elsewhere. The patient had no cough and there were no clinical signs of involvement of the lungs although an X-ray (Fig. 1) showed that there were multiple secondaries in the lungs. The patient was transferred to Chelsea Hospital for Women as previously arranged, although it was realized that the prognosis was practically hopeless. From the 18th to the 25th March, she was treated on the 400 K.V. X-ray machine and a dose of 1,250 r. was given direct to a perineal field. This was to have been followed by radioactive phosphorus but the patient's condition deteriorated rapidly and she died on 1st April, 1954, 15 weeks after the onset of bleeding and 9 weeks after the operation.

Hormone assay. On the 17th March the Friedman test was positive in a 1 in 1,500 dilution of serum. The cerebrospinal fluid was negative by the male toad test.

Pathology

Operation Specimen (Dr. Magnus Haines). The uterus received already opened and fixed measured 15 cm. (approx.) in length. Embedded in its anterior wall there was a spherical, spongy and haemorrhagic tumour about 8 cm. in diameter (Fig. 2). Part of the tumour protruded into the uterine cavity. The remainder of the endometrium was not remarkable. The Fallopian tubes appeared normal. The left ovary was fibrotic and the right ovary was not enlarged.

Histology. The tumour area showed numerous clusters of Langhans' trophoblast cells invading the myometrium. Cell groups were present within venous spaces (Fig. 3). Syncytial cells were also present in a few areas. In the muscle there was considerable necrosis and haemorrhage associated with areas of tumour cells. The adjacent endometrium showed decidual reaction. The glands appeared atrophic with slight chronic inflammation. The right ovary showed only fibrosis.

Autopsy (Dr. H. P. Ferreira). Locally there was a large mass of malignant tissue occupying the full length of the vagina. Para-aortic lymph nodes showed slight enlargement. Infarction was noted in the spleen and left kidney. Numerous

mottled dark red deposits were found throughout the substance of both lungs, in bronchial lymph nodes, in the thyroid gland and in the cerebellar hemispheres. Both cerebral hemispheres showed multiple deposits in the grey and white matter. There was one small deposit just beneath the ependyma of the posterior horn of the right lateral ventricle.

Histology. To confirm the autopsy appearances deposits of chorion-epithelioma were seen microscopically in the brain, cerebellum, thyroid (Fig. 4), spleen, left kidney, lungs and bronchial lymph nodes. No deposits were found in the para-aortic nodes.

Comment. The peculiar feature of this case is the development of a chorion-epithelioma of the uterus in a post-menopausal woman whose menstruation had been stopped by X-ray therapy 3 years and 4 months previously.

The origin of the tumour:

(1) The last previous pregnancy was 19 years previously at the age of 40 years. If the tumour arose as a sequel to this pregnancy it is one of the longest intervals on record.

(2) It is possible that the bleeding for which the X-ray therapy was given in 1950 was due to an incomplete abortion which was not recognized. This is unlikely as having had 8 children the patient would have recognized the symptoms of pregnancy. It is unlikely that the bleeding would have been controlled by X-rays if it had been due to retained products of conception.

(3) The patient could have become pregnant in her 59th year following an X-ray menopause.

It is well known that the ovaries may recover their function and pregnancy may occur without a menstrual period following the induction of an artificial menopause by irradiation. Pregnancy at the age of 59 years is not impossible but it is extremely rare. It should be pointed out that no evidence of a pregnancy was found on opening the uterus.

(4) The chorion-epithelioma could have arisen in a teratoma of the uterus. A teratoma of the uterus has not previously been recorded and no histological evidence to support the diagnosis of teratoma was found.

(5) The most plausible explanation is that the chorion-epithelioma arose in a uterus which had not been the seat of a pregnancy for 19 years and that the tumour was unconnected with the pregnancy.

Summary

A chorion-epithelioma in a female aged 59 years is described.

Her last known pregnancy was 19 years previously.

An artificial menopause had been induced by X-ray therapy 3 years and 4 months previously.

The possible origins have been suggested.

Acknowledgments

I wish to acknowledge the help and advice I have received in the preparation of this paper from Mr. A. F. Clift of the Mayday Hospital, and Mr. J. B. Blakeley, Dr. M. Lederman, Dr. M. Haines, and Dr. H. P. Ferreira of the Chelsea Hospital for Women.

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OVARIAN CARCINOMA ARISING IN AN ENDOMETRIAL CYST

BY

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THE tumours of the ovary have always aroused much interest and speculation due to their obscure histogenesis. The germinal epithelium is suspect in the majority of benign and malignant tumours, due to its potentiality for differentiation into various types of epithelium. For the past four decades ectopic endometrial tissue has also been repeatedly suggested as a potential source. Despite the fact that carcinoma develops frequently from the normally situated endometrium, it has always been found extremely difficult to prove such a source for the malignant growth in an ovarian endometrial cyst. The reasons for this are that ovarian carcinomas are symptomless in their early stages and by the time the patient seeks medical advice the benign ectopic endometrial tissue is completely replaced by the malignant growth. Secondly, even if both benign endometrial tissue and carcinoma can be shown in the same ovary, the latter can, on many occasions, be a metastasis from some other source. In consideration of these difficulties in establishing such an histogenesis, Sampson, who was the first to suggest this possibility, was led to lay down certain criteria. He postulated that in order to establish such an origin one should be able to demonstrate both cancer and benign endometrial tissue in the same ovary, and both should have the same relationship to each other as cancer of the endometrium of the body bears to the benign portions. Finally, he stressed that the carcinoma should arise in the ovary and must not invade it from another source. Fulfilling these criteria partially or completely, to the present, 27 such cases have been reported in the literature by Sampson himself (1925) and by various other authors (Tuthill, 1938; Teilum, 1944; McCullough *et al.*, 1946; Novak, 1947; Kuzma, 1947; Miller *et al.*, 1947; Rauramo, 1947; Moss and Runals, 1948; Corner *et al.*, 1950; Backer and Ambrose, 1951; Zilliacus and Widholm, 1952; Olsson, 1953; Fredrikson, 1953; Scott, 1953; Hunter and Klein, 1954).

A critical review of these cases reveals that the mere presence, in the same ovary, of both benign endometrial tissue and carcinoma is not, in itself, sufficient evidence that the latter arose from the former, as this association might conceivably be coincidence without causal relationship. Therefore, in order to rule out such an independent coexistence it becomes obligatory to demonstrate direct continuity between the benign epithelial lining of the endometrial cyst and the carcinomatous growth. Accordingly, we consider this to be one of the most important criteria in establishing such an histogenesis beyond further doubt. Accepting this, the number of undoubted cases becomes very small and are as follows: Sampson, one case; Tuthill, one case; Teilum, one case; McCullough *et al.*, one case; Novak, one case; Kuzma, one case; Miller *et al.*, one case; Rauramo, one case; Moss and Runals, one case; Corner *et al.*, two cases; Backer and Ambrose, one case; Olsson, one case; and Hunter and Klein, two cases, thus giving a total of 15 cases in all.

The carcinomas developing in ectopic endometrium are, in the majority of cases, adenocarcinomas. Other varieties encountered are adenoacanthoma, epidermoid carcinoma and

carcinosarcoma. The occurrence of acanthomatous lesions is, in Novak's opinion, additional evidence of the endometrial origin of certain of these growths. He based this assumption on the fact "such acanthomatous changes are practically never observed in the ordinary types of ovarian adenocarcinomas, while, on the other hand, adenoacanthoma is a relatively frequent form of endometrial carcinoma as observed in the uterus itself". However, this fact should be accepted with some reserve as a number of primary adenoacanthomas have been reported in the literature (Epperson and Benson, 1951; Kistner and Hertig, 1952).

The rarity with which all of the above mentioned criteria can be shown in a single lesion has prompted us to report such a case. An additional finding, which tends further to establish the thesis that the carcinoma arose from the pre-existing ovarian endometriosis, is the presence of typical endometrial stroma surrounding the frankly adenocarcinomatous areas.

Case Report

Mrs. L.C., aged 39 years, para 1+1, was admitted to Toronto General Hospital on 3rd November, 1954, with the complaints of a small lump in the lower left quadrant for the last 6 months, and intermenstrual dysmenorrhoea of 3-months duration. About 6 months ago she was also diagnosed as having one or several leiomyomata.

On examination at the time of admission the general condition of the patient was fair, and abdominal examination revealed a firm mass in the suprapubic region which was found to be mobile from side to side. A fair amount of tenderness was noticed in the left lower quadrant with an indefinite mass the size of an orange. On vaginal examination under anaesthesia a small leiomyoma in the lower uterine segment was felt, along with a cystic mass the size of a grapefruit in the left adnexa. At laparotomy, a diagnosis of leiomyomata of the uterus and endometriosis of both ovaries was made. A total hysterectomy, left salpingo-oöphorectomy, resection of right endometrial cyst, and appendectomy were performed.

On gross examination the uterus measured 11 cm. in length and 7·5 cm. in width, and revealed intramural and submucous leiomyomas, the largest measuring 2·5 cm. in diameter. The myometrium varied from 2 to 2·5 cm. in thickness while the endometrium was normal in appearance except for two pedunculated submucous leiomyomas, the larger of them measuring 1·5 cm. in diameter.

The left ovarian cyst measured 8·5×8×4 cm., the external surface of which was pinkish grey and smooth. At one pole part of the remnant of the ovary could be seen. On opening the cyst old haemorrhagic fluid was expressed and the internal surface was partly trabeculated. In a few areas it was brownish black and, arising from one pole of the inner wall, papillary projections were seen. These projections were friable and partly covered with haemorrhage. The largest of them measured 1·5 cm. in its longest diameter.

The right haemorrhagic cyst measured 2·5×1×0·2 cm., the internal surface of which was yellow in colour except at one place where there was evidence of old haemorrhage.

The left Fallopian tube and appendix were normal.

On microscopic examination, the left ovarian cyst was lined by normal endometrial tissue on the non-papillary surface, while papillary areas showed adenocarcinoma (Fig. 1). The areas of benign endometrium were characterized by a single layer of columnar epithelial lining, deep to which were also seen well formed acini lined by the same type of surface epithelium. These acini were surrounded by typical endometrial stroma (Fig. 2). In the adenocarcinomatous areas the glands were atypical, hyperplastic, and revealed a mild degree of anisocytosis and anisonucleosis (Fig. 3). These areas closely resembled adenocarcinoma of the body of uterus. In a few areas, typical endometrial stroma was present in the frankly adenocarcinomatous growth (Fig. 4), while, elsewhere, squamous metaplasia had occurred (Fig. 5). The most striking feature in this cyst was the continuity between the benign endometrial areas and the malignant growth, suggesting the origin of the latter from the former (Fig. 6).

The haemorrhagic cyst of the right ovary revealed endometriosis without malignant change.

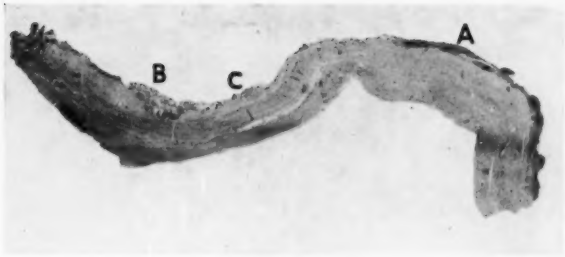

FIG. 1

Wall of the left endometrial cyst. The area marked "A" represents normal endometrial tissue. "B"—adenocarcinoma, and "C" area of continuity between benign endometrial tissue and the malignant growth.

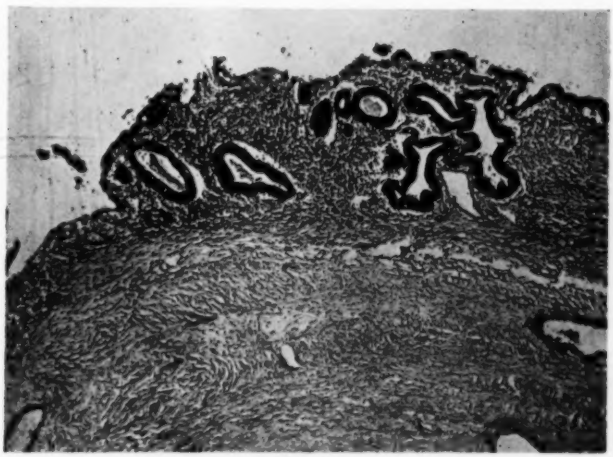

FIG. 2

High power view of areas of benign endometrial tissue (area A of the Figure 1).

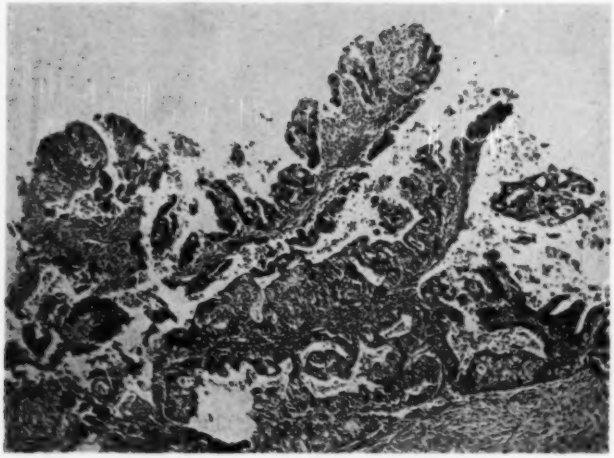

FIG. 3

High power view of adenocarcinomatous change in the wall of the cyst (area B of the Figure 1).

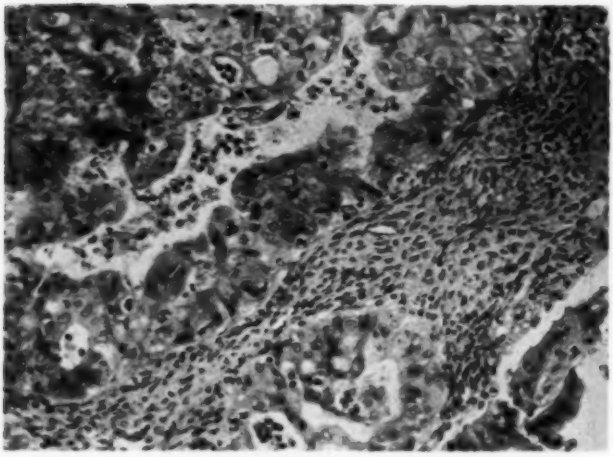

FIG. 4

Typical endometrial stroma surrounding the frank adenocarcinomatous growth.

D.K., W.A., D.V.W.

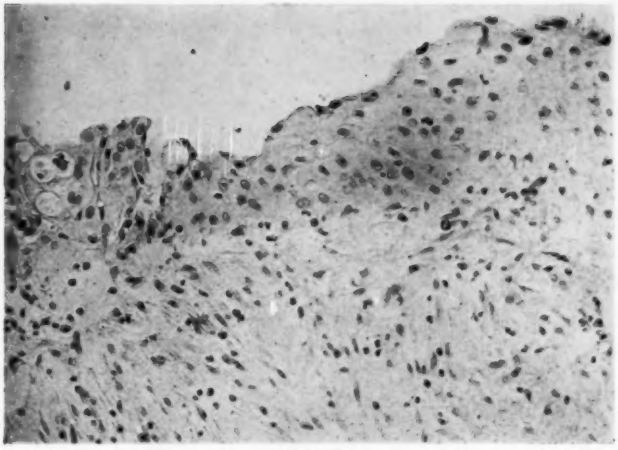

FIG. 5

Area showing squamous metaplasia.

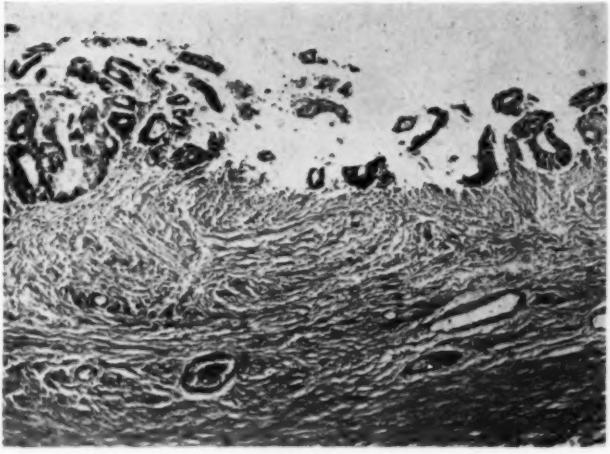

FIG. 6

Area of continuity between the benign endometrial tissue and the malignant growth (area C of the Figure 1).

In sections of the uterus submucous and intramural leiomyomas were present, along with a mild degree of endometrial hyperplasia.

The Fallopian tube and the appendix were normal.

Diagnosis. Adenocarcinoma arising from an endometrial cyst of the left ovary; endometriosis right ovary; endometrial hyperplasia (mild); submucous and intramural leiomyomata of the uterus.

Summary and Conclusions

(1) A case of ovarian carcinoma arising from an endometrial cyst has been described.

(2) In establishing such an origin, apart from Sampson's three postulates, the most important single criterion should be the demonstration of the continuity between the benign endometrial tissue and the malignant growth.

(3) The presence of typical endometrial stroma in frankly adenocarcinomatous areas is further suggestive evidence in establishing such a thesis of histogenesis.

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ENDOMETRIOSIS: THE RESULTS OF CONSERVATIVE SURGERY

BY

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THE treatment of endometriosis during the past 40 years has undergone changes which have reflected current knowledge of the nature of the disease. Before 1921 when Sampson first provided an explanation of the pathogenesis, the surgical treatment of endometriosis was largely conservative. Chocolate cysts of the ovaries were removed but ovarian tissue and the uterus were conserved when possible at all ages. Sampson (1921) showed that these lesions underwent cyclical changes depending on ovarian activity. While not condemning conservative surgery outright, he considered it was unwise and advocated removal of both ovaries and the uterus as the safest procedure. Subsequently the pendulum swung in the opposite direction and radical surgery for endometriosis was widely practised during the next decade.

In 1929 Read and Roques at the Royal Society of Medicine and Wharton in America reported satisfactory results following conservative surgery in young women with endometriosis. In addition to a high rate of symptomatic relief, several instances of pregnancy following operation were recorded. Gradually a more rational outlook towards endometriosis developed and the preservation of reproductive function with the relief of symptoms has now become the first principle in the treatment of younger women, radical surgery being reserved for older patients or those no longer wanting children.

In recent years the medical treatment of endometriosis with androgens, oestrogens and other drugs has gained popularity with the result that fewer cases are now being operated on. Numerous papers have been published in America in which equally good results are claimed for medical and conservative surgical treatment.

The present investigation was prompted by the fact that no reports have appeared in the British literature during the past 25 years on the results of the conservative treatment of endometriosis in this country. It was, therefore, decided to carry out a long term follow-up of patients who had been treated for endometriosis by conservative surgery.

MATERIAL

For the purpose of this study, conservative surgery was defined as an operation for endometriosis in which ovarian tissue was conserved. Between 1st January, 1943 and 31st December, 1948 100 patients were so treated at the Birmingham and Midland Hospital for Women and an attempt has been made to follow-up all these cases. The follow-up interval, therefore, varied from 6–11 years.

The diagnosis of endometriosis was confirmed in each case by histological examination of tissue removed at operation. This criterion was considered essential because other lesions are easily mistaken for endometriosis on naked-eye examination.

METHOD OF FOLLOW-UP

In the first instance all the patients were written to inviting attendance for interview.

Abdominal and pelvic examinations were carried out on all those who attended. To those patients who were traced but who were unwilling or unable to attend, a questionnaire was sent to obtain the necessary information.

Classification of Operation

In order to evaluate the results of the follow-up the operations performed were divided into 3 groups in Table I.

Table I

	Operative Procedures	No. of Cases
Group I	Resection of pelvic endometriosis preserving reproductive function	85
Group II	Total hysterectomy conserving ovarian tissue	9
Group III	Excision of extra-abdominal endometriomata	6
	Total	100
	Concurrent Procedures	
	Ventro-suspension	20
	Myomectomy	7
	Salpingostomy	1
	Resection of large bowel ..	2

Results

A total of 57 of the original 100 patients were successfully followed-up. Of these, 36 attended for interview and examination and completed questionnaires were returned by a further 21.

The success of the conservative operation was assessed in 3 ways:

(1) The absence of symptoms of endometriosis.
(2) The absence of physical signs of endometriosis (in those examined).
(3) The subsequent fertility of the patient (when reproductive function was preserved).

Group I. Resection of Pelvic Endometriosis Preserving Reproductive Function

The various operative procedures which were used are shown in Table II. These consisted mainly in removal or resection of ovaries diseased by endometriosis. In 3 cases the ovaries were unaffected and endometriosis in the pouch of Douglas was excised. This was infiltrating the bowel in 2 cases and bowel resection was undertaken.

Table II

Group I. Resection of Pelvic Endometriosis Preserving Reproductive Function

Procedure	No. of Cases
Unilateral oöphorectomy	37
Unilateral ovarian resection	15
Bilateral ovarian resection	12
Unilateral oöphorectomy with resection of other ovary	18
Resection of pouch of Douglas endometriosis	3
Total	85
No. of cases followed up	46 (54 per cent)

Effect on Symptoms. Of the 85 cases in Group I, 46 (54 per cent) were followed up and their symptoms assessed. The results are shown in Table III.

Table III

Group I. Effect on Symptoms

Result	No. of Cases
Completely cured of symptoms ..	32 (70 per cent)
Mild recurrence of symptoms ..	7 (15 per cent)
Severe recurrence of symptoms (further treatment undertaken) ..	7 (15 per cent)
Total	46

The interval between operation and the recurrence of symptoms of endometriosis and the severity of the symptoms showed interesting variations. Ten of those with further symptoms developed them within a year of the original operation while 4 patients developed symptoms 3–8 years after operation. In only 7 cases, however, was it necessary to undertake further treatment for in the remaining 7 the symptoms were not severe and responded to reassurance and medical treatment.

As was expected the younger age groups were more liable to recurrence than the older patients. This is shown by Table IV in which the low rate of recurrence in patients over 35 at operation

contrasts strikingly with the high rate of recurrence in those under 26.

TABLE IV

Recurrence Related to Age at Operation

Age group ..	21–25	26–30	31–35	36–40	Over 40
Cured	3	12	11	4	2
Recurrence ..	4	5	4	1	0
Total	7	17	15	5	2

Effect on Physical Signs. Abdominal and vaginal examinations were carried out on 29 (63 per cent) of the 46 patients in this group of cases who were followed up. These included 5 patients in whom further treatment for recurrent endometriosis had been necessary. In these there were no abnormal findings except for a painless indurated area in the recto-vaginal septum of a patient in whom recurrent endometriosis had been treated by radium.

Of the remaining 24 patients who were examined, 6 complained of symptoms suggestive of recurrent endometriosis but physical signs of recurrence were found in only 2 of them. One patient who was completely free of symptoms was found to have a tender, enlarged and cystic left ovary suggestive of recurrence. In the remainder no tenderness, nodules or swellings of any sort were found.

TABLE V

Summary of Recurrences

		No. of Cases
Recurrence treated		7
Untreated	Symptoms and signs of recurrence	2
	Symptoms without signs of recurrence	4
	Signs of recurrence without symptoms	1
	Symptoms of recurrence (not examined)	1
Total		15

Inclusive recurrence rate: 33 per cent.

A summary of all the cases with a possible recurrence of endometriosis is presented in Table V. The total recurrence rate of 33 per cent probably errs on the pessimistic side since 4 cases are included in whom no definite signs of recurrence were found despite suggestive symptoms.

Predisposing Causes of Recurrence. Since 6 of the 7 patients with recurrences severe enough to require further treatment had to have it within 10 months of the original operation, it seemed worthwhile to seek a cause for the failure of conservatism in these cases. The operation notes of 5 of them recorded that all foci of endometriosis had not been completely removed originally, small areas being left either in the pouch of Douglas or on one ovary. Foci had also been left in 2 other patients who had developed recurrent symptoms but who did not need further treatment. The operation notes of those patients permanently cured showed that in only 1 of them had a small area of endometriosis been left behind, although in many the disease had been very extensive originally. It seems probable, therefore, that more complete excision of endometriotic foci in the failed cases would have reduced the recurrence rate.

Treatment of Recurrences. The procedures carried out in the 7 patients with recurrence severe enough to need more radical treatment consisted of:

Total hysterectomy and oöphorectomy	3
Radium menopause	3
X-ray menopause	1

These procedures, as stated above, were carried out within 10 months of the original operation with the exception of 1 case in which hysterectomy was performed 7 years afterwards. Another patient in the series had a hysterectomy for dysfunctional menorrhagia 5 years later but no evidence of further endometriosis was found at the second operation.

It was noted that 3 of the 4 patients who were given radiotherapy were under 30 at the time and each suffered severely from menopausal symptoms. The other was 39 and she did not complain similarly. Of those treated by hysterectomy and oöphorectomy 2, who were under 30 at the time, complained of menopausal symptoms but these were of a mild nature.

Subsequent Fertility. In assessing the fertility rate following operation, certain patients in

whom pregnancy was considered most improbable were excluded as shown in Table VI. This was done in order to make the final figure comparable to fertility rates quoted in other follow-ups of a similar nature.

TABLE VI
Fertility after Operation

Cases excluded:	
Over 40 at operation	3
Remained single	7
Contraception used	1
Total remaining with prospect of pregnancy ..	35
Total becoming pregnant	16

Pregnancy rate: 45·7 per cent.

Thirty-five patients were considered to have a reasonable prospect of pregnancy after operation and of those, 16 (45·7 per cent) became pregnant. The total number of babies born was 24 of which 1 was stillborn. One patient had 3 pregnancies, 6 had 2 pregnancies, and 9 had a single pregnancy. None of those followed up had any miscarriages.

The age at the time of operation of those patients who subsequently became pregnant is shown in Table VII compared with the total number who were considered to have some prospect of pregnancy.

TABLE VII
Fertility Related to Age at Operation

Age Group	21–25	26–30	31–35	36–40
No. becoming pregnant	3	8	3	2
No. with prospect of pregnancy	6	15	11	3

Although the figures are too small to be of any great significance they suggest that there was an encouraging prospect of pregnancy in all the age groups. Factors favouring conception were difficult to determine from the information available on these patients. Infertility had not been the primary complaint of any of them and fertility investigations were not embarked upon. The extent of the disease did not, however, appear to prejudice the prospects of pregnancy for in half those subsequently becoming pregnant endometriosis had been present in both ovaries and bilateral resection had been performed. In one patient, who also had multiple fibroids, endometriosis was infiltrating the recto-sigmoid junction causing a stricture. Myomectomy and ventrosuspension were performed followed by resection of the affected portion of bowel and an anastomosis. This patient had 2 normal deliveries during the next 3 years.

Retroversion when present was corrected in all cases at operation but those patients in whom ventrosuspension was performed did not show a pregnancy rate higher than those in whom the uterus had already been in the anteverted position at the time of operation.

Although 3 patients developed symptoms suggestive of recurrent endometriosis after pregnancy, examination failed to reveal any confirmatory signs in the pelvis. This did not, however, exclude the possibility of the disease being present.

Group II. Total Hysterectomy Conserving Ovarian Tissue

There were 9 cases of endometriosis in this group of whom 6 were followed up. The group is small because the large majority of patients, in whom hysterectomy was performed for endometriosis, had both ovaries removed at the same time. The ages of the 6 patients at operation ranged from 34–53 years. One had died from unknown causes but the remaining 5 were well and free of symptoms. All were examined and no evidence of recurrent endometriosis was found. Although ovarian tissue had been preserved in these patients with the object of preventing the onset of acute menopausal symptoms, 1 of them had in fact suffered from quite severe symptoms shortly after operation. It seems probable that in this case impairment of the blood supply of the remaining ovarian tissue had caused it to atrophy.

Group III. Resection of Extra-abdominal Endometriomata

There were 6 cases of endometriosis in this group of whom 5 were followed up. The sites of the lesions and the ages of the patients are shown in Table VIII.

TABLE VIII

Group III. Resection of Extra-abdominal Endometriosis

Site of Lesion	No. of Cases	Age at Operation
Perineum	1	48
Vulva	1	31
Vagina	1	21
Round ligament	2	31 and 41
Umbilicus	1	44
Total	6	
Total followed up	5	

At the time of the original operation there was no evidence in these patients of pelvic endometriosis and the operations consisted of simple excision of the endometriomata. At the follow-up 1 patient complained of symptoms suggestive of recurrence of an umbilical endometriosis but she did not attend for examination. The remaining 4 cases were free of symptoms and 2 who reported for examination had no signs of endometriosis either at the site of the original lesion or within the pelvis. Of 2 patients in this group, who were married and under 41, 1 had become pregnant and been delivered normally.

Table IX is shown below to compare the figures resulting from the present follow-up with those in previous series.

DISCUSSION

Endometriosis is a disease upon which it is impractical to generalize with regard to treatment because each case presents an essentially individual problem. For young women, however, and older women still wanting children the first principle must be to relieve symptoms while preserving the child-bearing ability. That this can be achieved in a high proportion of cases has been shown by this follow-up of cases treated by conservative surgery.

Although 15 per cent of the cases in Group I later required more radical treatment this figure might have been smaller if all foci of endometriosis in the pelvis had been eradicated at the time of the original operation. It is not by any means possible to do this by conservative procedures in all cases of endometriosis. While chocolate cysts can usually be enucleated and other foci in the ovaries resected leaving sufficient ovarian tissue for physiological function, peritoneal implants may present a technically more difficult problem. It is of interest that Novak (1936), Beecham (1949) and, more recently, Brewer and Maher (1954) advise leaving these implants in the belief that they will not cause symptoms. Meigs (1949), however, recommended that they should always be removed surgically or destroyed by cautery. The cases followed up in the present investigation support his belief that they may cause trouble for several patients in whom they were left required further treatment within a year. The most difficult problem is presented by endometriosis in the recto-vaginal septum, often associated with dense adhesions in the pouch of Douglas and conservatism in such cases may be hopeless. To

TABLE IX

Comparison of Results
Conservative Surgery Preserving Uterus and Ovarian Tissue

Author	Year	No. of Cases	Relief of Symptoms (expressed as percentages)			Pregnancy Rate (per cent)
			Cured	Improved	Failed	
Read and Roques	1929	14	71·5	19·2	9·3	0
Keene and Kimbrough	1930	21	95·3	4·7	0	28·0
Pemberton	1937	107	71·0	—	29·0	15·0
Counseller	1938	98	56·2	19·8	24·0	6·0
Holmes	1942	24	29·1	54·1	16·6	12·6
Bacon	1949	138	49·3	21·0	29·7	26·8
Beecham	1949	43	95·5	—	4·5	37·0
Counseller and Crenshaw ..	1951	48	60·0	28·0	12·0	20·8
Present Series	1954	46	70·0	15·0	15·0	45·7

excise all the endometriosis may be technically impossible without damaging the rectum or removing the uterus and hysterectomy with removal of the appendages is often necessary to effect a cure. Presacral neurectomy as an adjunct to the conservative surgery of endometriosis is popular in America but it was not performed in any of the cases under review. To be effective the nerve fibres in the ovario-pelvic ligaments should also be divided and this must impair the blood supply of the ovaries to some extent.

In younger patients it is probably better to err on the conservative rather than the radical side when operating. The need for a later more radical operation does not necessarily reflect discredit on the conservative procedure for time and possibly a pregnancy may have been gained meanwhile. It was found in the present study that the relief of symptoms and subsequent fertility of patients treated by the more extensive conservative procedures was quite equal to that resulting from smaller operations for single foci of endometriosis. This confirms some similar observations made by Bacon (1949) and Siegler and Bisaccio (1951) and is an important point to bear in mind when making a prognosis.

It must be emphasized that, although the present fertility rate of 45·7 per cent compares favourably with other reported figures, these patients were not operated on primarily for infertility but for other symptoms related to endometriosis. Some of them might have become pregnant without operation but it is probable that operation improved their prospects and, because conservative rather than radical surgery was employed, 45·7 per cent achieved pregnancy while 70 per cent had permanent symptomatic relief.

It is doubtful if these results could be equalled by medical treatment alone although some authors (Counseller and Crenshaw, 1951; Siegler and Bisaccio, 1951) believe that the fertility rate is no better with surgical than medical treatment. It is true that, if operation can be postponed and pregnancy occurs, temporary and sometimes permanent relief of symptoms may follow but pregnancy does not necessarily ensure against recurrences. The activity of the disease and the severity of the symptoms will often demand early operation although in the milder cases hormonal treatment may be given a trial. It must be remembered, however, that in some cases in which medical treatment has been tried and has failed the disease has meanwhile become too extensive for conservative surgery.

Assessments of the value of the medical treatment of endometriosis are usually unsatisfactory because the accuracy of the diagnosis is seldom confirmed by operation. The clinical diagnosis of endometriosis does not always follow textbook lines. Extensive but inactive lesions may be relatively symptomless, small active lesions can cause severe symptoms while other pathological conditions can closely simulate endometriosis. Hofmeister and Grinney (1952) compared the pre-operative diagnosis of endometriosis by themselves and others with the conditions found at operation and reported that diagnostic accuracy varied from 20–51 per cent. When, therefore, Counseller and Crenshaw (1951) state that only 25 per cent of patients with endometriosis at the Mayo Clinic are operated on, the results claimed for medical treatment must be accepted with some reserve.

When radical surgical treatment is decided upon, removal of the uterus and any remaining ovarian tissue has for long been the accepted procedure. Induction of the menopause by radiation has become less popular than previously in view of the undesirable after effects and most gynaecologists now prefer the surgical approach. Opinion is divided on whether complete extirpation of all ovarian tissue is necessary to prevent recurrence of endometriosis providing the uterus and all endometriotic lesions are removed. Cashman (1945) followed up 85 cases treated in this manner with preservation of ovarian tissue and he found evidence of recurrence in none of them. He suggests that a break in the "pituitary-ovarian-endometrial" relationship by removing the uterus is as effective in preventing recurrence of endometriosis as removal of the oestrogenic stimulus. The small group of cases in the present series which were treated by hysterectomy leaving some ovarian tissue lend some support to this view for no recurrence was found in them. By this procedure the acute menopausal symptoms which may follow castration can be avoided with the knowledge that surgery has been as radical as necessary.

The cases of extra-abdominal endometriomata followed up in this investigation were too few to form the basis for significant conclusions. They are uncommon lesions and in these cases did not appear to be associated with pelvic endometriosis at the time of the original operation or subsequently. The treatment of choice is undoubtedly local excision.

Summary

(1) Fifty-seven patients treated for endometriosis by conservative surgery between 1943 and 1948 were followed up in order to discover the incidence of recurrence of the disease and their subsequent fertility rate.

(2) Of 46 patients with pelvic endometriosis in whom the uterus and ovarian tissue was conserved, 70 per cent obtained complete relief of symptoms. Mild recurrence was present in 15 per cent and recurrence needing further treatment in 15 per cent also. More complete removal of all foci of endometriosis at operation would probably have reduced the recurrence rate.

(3) Of 35 patients with pelvic endometriosis in whom reproductive function was preserved, 16 (45·7 per cent) became pregnant, producing 24 children. The fertility rate was not appreciably influenced by the extent of the operation or the age of the patient when under 41 years.

(4) Follow-up of those in whom recurrences had been treated suggested that surgery was preferable to radiotherapy in women under 30 because of the severe menopausal symptoms associated with the latter.

(5) No evidence of recurrence was found in 5 patients in whom endometriosis had been treated by hysterectomy preserving ovarian tissue. It is suggested that, if radical surgery is indicated, complete castration is not necessary topre vent recurrences, providing the uterus is removed.

(6) Five cases of extra-abdominal endometriomata showed no evidence of pelvic endometriosis either at operation or subsequently and were treated by simple excision of the lesion.

(7) The significance of the results of the follow-up is discussed and views are expressed on the various surgical procedures employed and the place of medical treatment.

We should like to express our thanks to the Consultant Staff of the Birmingham and Midland Hospital for Women for permission to follow-up their cases and for their encouragement.

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CORRELATION OF PLACENTAL ANOMALIES WITH SPONTANEOUS ABORTION OR PREMATURE SEPARATION

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THE placenta is the root structure of the foetus. In it is printed a fantastic story for anyone with the eyes to read. To the untrained the soil in the floor of an ancient cave means little; to the trained archaeologist with minute analysis of each succeeding layer there is unfolded the centuries' old history of the occupants. With like observation and training, mostly self-training, a student may by reading aright the signs in the individual placenta know much about the life history of the foetus in question and indeed of its mother and her previous and subsequent pregnancies.

Certainly in this broad land there are many physicians who have the urge to make some original investigations or observations and thereby pay, in part, the debt for all the accumulated knowledge passed on to them. They may thus rightfully join the fraternity of those who produced the knowledge. Probably many a one goes through life somewhat frustrated for the want of a problem upon which to work.

The object of this paper is to present a relatively simple procedure whereby a physician may with little time enlarge upon his appreciation of the human placenta; upon what the various forms mean; possibly add to the general knowledge and at the same time explore a world few have ever seen. The results of this method are quite obvious to anyone inasmuch as the foetal sac is reconstructed to the intra-uterine size and shape and may thus be viewed from any aspect, inside or out.

The equipment consists of (*a*) an aquarium (Fig. 1) 12×16×18 inches with basal drainage and an overflow at 14-inches height; (*b*) a 9 litre graduate (10 cm., 50 cm., 100 cm.), measuring 4·5 inches in diameter, by 40 inches, constructed of copper sheeting or possibly plastic tubing, closed at top and bottom with inlets and outlets as illustrated. The inlet at the top is permanently connected to the cold water pipe of the city water supply so that when the tank is filled the graduate is automatically filled. Above the aquarium is a standard arm, elevatable, for holding four plastic clothes pins to which the open end of the foetal sac is attached. The collapsed sac is then distended by water drawn from the bottom of the graduate so that the amount to fill it may be readily determined. The distended sac may then be turned from side to side for photographing or for viewing in constructing a wet clay model of it with the placenta outline demarcated and painted on. The amount of clay by weight bears a direct proportion to the quantity of water required to fill the sac, 3 g. per 100 ml. The ordinary commercial potters clay may be purchased in 25-pound lots and kept in a 20-gallon straight sided jar with a relatively air tight, foot-lifted lid. One will find that 25 per cent or more of all term placentas or abortion sacs will be fit to study by this method. This depends upon the care taken in delivery. The others have the sac torn so that no such study is possible. Abortion sacs of larger size may be studied as above but a more exacting investigation is as follows: the sac carefully handled and washed in running water is then suspended in a cube shaped glass jar (Fig. 2) or a small fish aquarium and the sac is filled with plain gelatin solution which is then hardened in a refrigerator with the sac distended in the water or saline solution. To facilitate this procedure one should have a number of ordinary

operating room skin clips. Six or eight inches of small size catgut is tied to the middle of each clip. A clip is attached to the margin of the rent in the sac and followed by 3 others equidistant around the opening. The gut strings pulled over each of the 4 walls of the jar are held by scotch tape. With the tank ¾ full of water or normal salt solution the gelatin is thus introduced after the fluid in the sac has been sucked out. The margin of the opening in the sac is maintained slightly above the level of the fluid in the tank. The gelatin may be purchased at the grocery store and each package contains 4 envelopes. Each of the latter makes enough solution to fill at least 2 sacs. The gelatin powder is put in a small quantity of cold water and boiling water

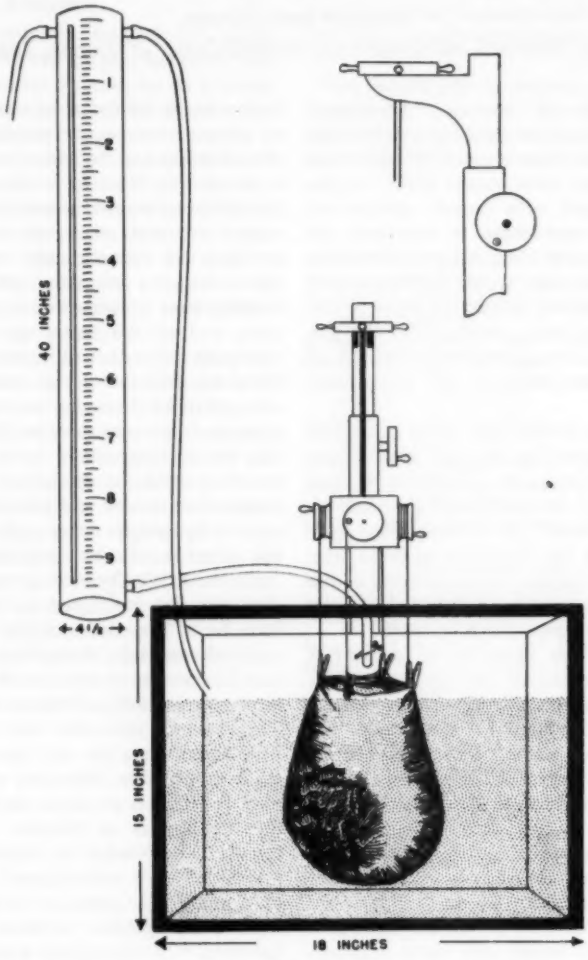

FIG. 1

Apparatus for placental sac study by fluid distension in a tank of water.

is added enough to fill the sac but one should allow the solution to cool before pouring it into the amniotic cavity. After hardening in the refrigerator overnight the loose decidua is replaced over the sac as it was in the uterus and then the whole specimen is removed and fixed in formalin in a storage jar for future study.

The best method is to study each placenta possible immediately following delivery while the history is fresh in mind or easily obtained. This requires only a few minutes. If a clay model were made for each one available there would be a collection of 250 or more for each 1,000 deliveries. It may be that careful delivery of the placenta without twisting would produce many more intact sacs. Furthermore, careful observation at the time of delivery determines to which wall the placenta was attached. To begin to appreciate the value one must make the study more or less routine and keep accurate records which may be tabulated for results. Placentas wrapped in a damp towel will keep fresh for study in a refrigerator for a week or more. It is desirable for every hospital delivering 1,000 babies a year to have such equipment installed at the end of a sink near the delivery room where records could be made. Within a very few years the accumulated information, I am sure, would amplify and modify our fundamental knowledge of human pregnancy and elucidate many clinical features now little understood. From a study of approximately 1,200 such models made from 1936 to 1941 the following conclusions have been derived: The uterine cavity at the time of implantation has a triangular anterior flat wall opposing a posterior one of equal size. At the margins is an acute angled crease. When the egg implants, if it should lie in this crease, a portion of the resulting placenta lies upon one wall and the rest lies upon the opposite wall so that the placenta is bilobate as a rule: this occurred in 8 plus per cent of the models. Three hundred and fifty-five of these have been previously reported and many of them illustrated as to intra-uterine site. These two walls may generally be identified in the distended sac because the sac assumes the intra-uterine shape presenting in most cases bulges at the uterine horn areas. One then can usually identify anterior or posterior wall but is seldom able to distinguish one from the other. Of the 91 per cent of placentas not bilobate the implantation is as a rule on the relatively flat surface and usually near the centre of the anterior or posterior triangular wall, probably a few per cent more often on the posterior wall. These placentas then are usually discoid and cover approximately one-fourth of the surface of the sac at term. A few are definitely cornual. Roughly 60 per cent of them had normal edge, 36 per cent had marginate infarction edge, and 1 per cent had circumvallate edge. Extremely rarely there is one placenta (primarily) on one wall and a smaller secondary or succenturiate one, opposite, on the other wall. This is most certainly due to superficial implantation of the ovum so that the usual decidua capsularis of the human is lacking and the abembryonic pole of the ovum erodes and attaches to the opposite wall. This is similar to the usual monkey implantation (Ahlfeld, 1911; Wislocki, 1929; Mossman, 1937).

An important observation in regard to the series of models is that in abortion sacs the area of the placenta in relation to the area of the sac is much greater than that of term placental sacs. This caused considerable speculation until it was realized that there must be some method of nature in reducing the relative size of the excessive placenta as pregnancy progresses. If the discoid placenta originally covers $\frac{1}{4}$ of the sac surface, it and the area of the uterine wall to which it is attached increase in size simultaneously without marginal stress or strain and a normal edged placenta results.

If the discoid placenta originally covers more than $\frac{1}{4}$ and up to $\frac{1}{2}$ of the ovular sac the excess over $\frac{1}{4}$, unable to spread as fast as the uterine wall, is gradually separated, becomes atrophied and is laid down around the placental margin in a white marginate border. This explains why there are reflexed layers of decidua between the placental margin and the atrophic peripheral villi. The partial or total white margined type of placenta was named placenta marginata by Koelliker (Koelliker, 1879; Schwarz, 1938; Geisendorf, 1949; Rumbolz and McGoogan, 1953; Williams, 1927; Kustner, 1884; E'Ibarguengoitia, 1909).

Furthermore, if as rarely occurs the original placenta covers more than half of the early ovular sac then it is necessary for a ring to form and thus gives rise to placenta circumvallata, 1 to 3 per cent. In extremely rare instances the whole sac is covered by placenta in which case abortion is quite inevitable at any time up to approximately 3½ to 4½ months. This has been designated placenta membranacea with an incidence of far less than 1 per cent.

As Wislocki (1929) has stated the human placenta originates from a diffuse chorionic villus structure over the whole circumference and becomes discoid secondarily by atrophy of the capsularis chorion in contradistinction to the primarily discoid shape of the monkey placenta (bidiscoid; one on each wall). All of these various types of discoid placentas are readily explained by a variation in depth of implantation of the fertilized ovum into the decidua; the most superficial being the double discoid or one with a very small single placenta, the abembryonic pole failing to attach to the opposite wall. This latter results in insufficient nourishment to the foetus which may die in pregnancy and abort or go to term with a scrawny poorly developed underweight foetus as has been described by Schwarz (1938), Geisendorf (1949), and Rumbolz and McGoogan (1953). Sixty per cent implant exactly enough to form a 25 per cent coverage of the ovular surface and go to term with a normal edged placenta. Thirty-six per cent implant deep enough to produce a marginate placenta with not infrequent abortion, or premature separation at or near term, but here most go to term with normal outcome and a placenta with the evidence definitely present in the marginal infarction which may embrace part or all of the circumference. From clinical studies I have concluded that 2 or 3 per cent of these abort and a few result in premature separation at or near term, which may be serious or merely a premature onset of labour with some slight haemorrhage during labour. It should be noted that some women are able to have perfectly normal pregnancy and labour with a well developed marginate or circumvallate placenta. In these cases the rupture of the fine decidual vessels takes place without much haemorrhage or effects thereof. The open capillaries may clamp down and prevent haemorrhage or the blood may clot rapidly.

The deepest implantation results in circumvallate or membranaceous placentas of which my clinical studies have indicated that 80 per cent of circumvallates and almost 100 per cent of membranaceous abort. If this is true, and there are approximately 40,000 term circumvallata placentas annually in the United States, there should be 160,000 spontaneous abortions associated with this anomaly. J. Whitridge Williams in 1927 concluded that placenta circumvallata had no clinical significance and most American textbooks tend to agree and consequently devote few lines to the subject. The following authors, however, have noted an associated tendency to intermittent haemorrhage and abortion: Kustner (1884), Schwab (1895), E'Ibarguengoitia (1909, quoting Roemer, Ferroni, Koch, Sfameni, Kroemer), Riehl (1924), Rueder (1933), Hobbs and Rollins (1934), Fauvet (1935), Hunt (1935), Hobbs and Price (1940), Hertig and Sheldon (1943), Hunt, Mussey and Faber (1947), and Paalman and Vander Veer (1953). Many other instances terminate in premature separation and haemorrhage with or without serious consequences to the foetus.

In a study of 38 consecutive abortion sacs it was found that 50 per cent were associated with such excess area of placental formation that they would certainly have been typical circumvallates if they had gone to term (Fig. 3). Furthermore, in a series of 48 consecutive premature placental separations it was noted that the haemorrhage was extra-placental and marginate in origin in placentas with marginate infarction in 80 per cent (5 circumvallates and 34 marginates) even in a few in which there was evidence of toxaemia. In some toxaemic patients the separation may occur in otherwise normal placentas in which the haemorrhage is inside of the placental tissue. It may be that there are at least three types of premature separation of the normally implanted placenta; (*a*) those from damage to the maternal placental vessels or sinuses associated with toxaemia of pregnancy or other conditions and (*b*) a larger group with or without toxaemia and due to rupture of marginal decidual vessels in marginate or circumvallate placentas. These

FIG. 2

Abortion sac suspended in saline solution and filled with gelatin.

FIG. 3

Early placenta circumvallata diagnosed as such before termination. Aborted at 4¾ months after prolonged vaginal bleeding throughout pregnancy. Foetus 530 g., C.R. 19½ cm., head B.P. diameter 5·5 cm. Placenta weight 257 g. Nearest placenta to sac rupture 6 cm.

FIG. 4

Many circumvallate placentas appear as above when the foetal sac is distended in a tank of water.

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latter may coincide with the pathology noted recently by Fish, Bartholomew, Colvin and Grimes (1951) as due to marginal sinus rupture, (*c*) a small but distinct group due to trauma.

Authors of various nationalities give credit to William Hunter for the first description in 1794 of marginate or circumvallate placenta but until 1927, when Williams published a comprehensive paper on placenta circumvallata, there was no paper by any author writing in English. In the meantime, however, there were upwards of a hundred publications mainly by German students of the subject. Several also were written by Italians, a few by French, and occasionally one by authors of other nationalities. One may enquire as to why the Germans did not devise a comprehensive explanation correlating all of these anomalies. There are probably several reasons; (1) they did not know much about the location of implantation in spite of a classic paper on the subject by Karl Holzapfel in 1898, who studied 107 sacs by a water distension method similar to the one herein described. None other made use of his method or paid much attention to his results except his son Guenther who in 1940 continued his work; (2) the German leaders of the time were quite thoroughly imbued with the relatively new idea of infection as the main aetiologic factor. Syphilis at that time created marked disturbances in the foetus and placenta; (3) many papers appeared based upon a single specimen and these authors were apparently more interested in clinical aspects than in attempting to give a rational explanation; (4) during this time little was known about early human ovular implantations inasmuch as few had been published. Peters ovum appeared in 1899. Lahm in 1924 presented the idea of deep endometrial implantation for the explanation of circumvallata but this was rejected by Williams three years later.

It is hoped that this discussion will stimulate interest in the further study of the ubiquitous, little understood and sadly neglected deciduous organ—the human placenta.

I owe a debt of gratitude to the colleagues, residents, interns, medical students and nurses who were on the look out for and helped collect material for this study and to the translators of the foreign language papers—Dorothea Steffan Dawson, Margaret Peters Evans and Ruth Stone.

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PLASMA AMINO-ACID LEVELS FOLLOWING PROTEIN INGESTION BY PREGNANT AND NON-PREGNANT SUBJECTS

BY

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INTRODUCTION

CRAMER and Winnick (1943) found no significant difference between the fasting plasma alpha-amino-nitrogen levels of normal men and women: they gave 4·2 mg./100 ml. as the mean fasting value.

Bonsnes (1947) showed that pregnant women have a lower plasma alpha-amino-nitrogen level from the ninth week of pregnancy until term (average 3·2 mg./100 ml.) than the non-pregnant subject (average 4·3 mg./100 ml.).

Christensen and Streicher (1948) suggested that this was due to the active transfer of amino-acids to the foetus, as they found the plasma level to be higher in the foetus than in the mother.

Crumpler, Dent and Lindan (1950) confirmed Christensen and Streicher's findings. Using paper chromatography, they found all the individual amino-acids of the maternal plasma, as well as the total alpha-amino-nitrogen level, at a higher concentration in the foetal plasma.

In our own studies (Clemetson and Churchman, 1954) we found that, while the foetal/maternal alpha-amino-nitrogen ratio was 1·65/1 when foetal and maternal blood samples were collected at normal deliveries, this ratio fell to 1·38/1 when the umbilical cord was obstructed by being coiled round the foetal neck at birth. This change in the ratio is the result of a significant rise in the maternal level rather than a fall in the foetal level. Thus a premature cutting off of the amino-acid transfer, and/or utilization by the foetus, causes the low maternal level to rise towards the non-pregnant level, which Bonsnes has shown that it normally reaches a day or two after delivery. This is taken as evidence that the cause of the low pregnant level is the active transfer of amino-acids to the foetus.

Losee and Van Slyke (1917), using the Van Slyke (1912) method, were probably the first to study the amino-acid levels in toxaemic women. They reported that not a single one of 10 eclamptic women whose blood was examined showed a figure outside the range noted by other workers in the blood of normal *men*: the proper control study of normal pregnant women was lacking.

Recent work by Burt and Kimel (1953), using the ninhydrin manometric method, is inconclusive. The levels in their charts agree closely with our own (Figs. 1 and 2), and show the alpha-amino-nitrogen level of ante-partum pre-eclamptic women to be above the level of normal pregnancy, but their tables, which concern two other groups of women, do not show this difference.

Our own findings in severe pre-eclampsia were very similar to those of "cord obstruction" in that the foetal/maternal amino-acid ratio fell from the normal of 1·65/1 to 1·37/1, and the maternal plasma alpha-amino-nitrogen level rose from 2·96 to 3·52 mg./100 ml., thus approaching the non-pregnant level.

We have argued that these changes in pre-eclampsia might be due to a decreased transfer of amino-acids to the foetus, to a decreased utilization of amino-acids by the foetus, or to a

combination of these two factors; this has been postulated because of the close similarity of the results to those obtained in a group of normal deliveries where the umbilical cord was obstructed. It is, however, possible that these results reflect an alteration in the maternal nitrogen metabolism.

Present Investigation

The work reported here is a further enquiry into the nature of the low plasma amino-acid level of pregnancy.

If this low level is due to the active transfer of amino-acids to the foetus, is it only the fasting level that is lower, or does the pregnant woman have a generally lower level? Does the plasma amino-acid level fall more rapidly in the pregnant subject after a protein meal, or is the absorption curve generally depressed?

To answer these questions two methods were adopted: firstly, random samples from pregnant women and from normal men and women were analyzed; and, secondly, amino-acid levels following protein ingestion were estimated.

The amino-acid curves reported by West, Wilson and Eyles (1946) in children, using 1·7 g. of *Casec* per kilo body weight, lasted only 5 hours, but, using a similar dose (1·5 g. per kilo of pregnant weight or 2·0 g. per kilo of pre-pregnant weight), viz. 100 g. of a similar calcium caseinate preparation (*Casilan*) in a pregnant woman (Case N.), we found that the plasma amino-acid level had barely started to fall after reaching its maximum in this time.

When possible we prolonged subsequent tests to 24 hours so that the full curve should be obtained, but the unexpected form of the early part of the curve found in duplicate estimations of this first case led us to continue to take more frequent samples during the early period even when the full 24 hours was being studied.

Neither the pregnant nor the pre-pregnant weight seemed suitable for calculating the size of test meals for pregnant subjects, as both have their disadvantages when the results are to be compared with those obtained on non-pregnant subjects. In view of this, every patient was given the same test meal irrespective of body weight.

Our choice of subjects was limited by their availability, and by their willingness to undergo such a prolonged test; the 12 volunteers comprised 4 normal men, 4 pregnant women and 4 *post-partum* women, but of the pregnant women only 2 were normal.

Method

The test meal consisted of 100 g. of *Casilan* (Glaxo), a preparation of calcium caseinate whose percentage composition is given as

Protein 90, Fat 1, Carbohydrate 1, Mineral Salts 4, Moisture 4.

To this was added 1 ounce of *Camp* coffee essence, and it was made up to 1 pint with water. The mixture was warmed and homogenized in a Waring blender to prevent it from setting as a gel at this concentration.

Samples of this mixture (as used for the tests) were analyzed, and the total free alpha-amino-nitrogen content of the meal was found to be 20·1 mg.

The subject was fasted overnight and a sample of blood was drawn from the antecubital vein in the morning. The test meal was then consumed in 15 minutes, and 7 further samples were collected at ½, 1½, 3, 4½, 6, 12 and 24 hours after completing the meal.

In one normal man (subject D) 15 samples instead of the usual 8 were collected during the 24 hours, to investigate the shape of the early part of the curve. This was facilitated by the introduction of a fine indwelling polythene tube into the cephalic vein.

All the blood samples in this and the other tests were collected in bottles containing 500 Toronto units of dry heparin, and were centrifuged within 15 minutes of collection; the plasma samples so obtained were stored at minus 10° C. until analysis.

During the 24 hours of the test the subjects were allowed as much fluid as they wanted to drink and were provided with glucose and fruit, but no food containing material amounts of protein was allowed.

Amino-acid analyses were carried out on 1 ml. samples of plasma by the ninhydrin carbon dioxide method of Hamilton and Van Slyke (1943).

Results

The analysis of random samples taken from 10 normal pregnant women admitted to hospital at term, just starting labour, compared with random samples from 5 normal men and 5 normal women showed very little overlap in the amino-acid levels of the two groups.

Table I

Plasma Alpha-amino-nitrogen Levels in mg./100 ml.

	Normal Non-pregnant	Pregnant At term
Men:		
	5·6	3·7
	4·5	2·6
	5·6	3·0
	5·0	4·7
	3·8	3·0
Women:		
	5·2	3·6
	5·7	2·6
	4·4	3·3
	4·9	2·7
	4·1	3·8
	Mean 4·89	Mean 3·30

Neither group was fasting, so the levels are not basal, but the difference found by Bonsnes is very evident.

The results of the protein ingestion experiments are plotted graphically as curves in Fig. 1.

Discussion

The curves typically have a steeply rising slope reaching a maximum at 3 hours, then falling more slowly back to the basal level in about 12 hours, but many variations are found. Some show a tendency to be biphasic in having a higher half-hour level than would be expected from the rest of the curve, and the constancy of the position of the minor peak so formed suggests that it is more than a chance effect.

One case (D), which does not show this half-hour peak when only the usual 8 points are considered as in Fig. 1, does show a tendency towards it in Fig. 2 where the results of more frequent samples are plotted.

An early rise in the amino-acid level such as this might be expected if the free amino-acid content of the test meal were high. The free alpha-amino-nitrogen content of the test meal

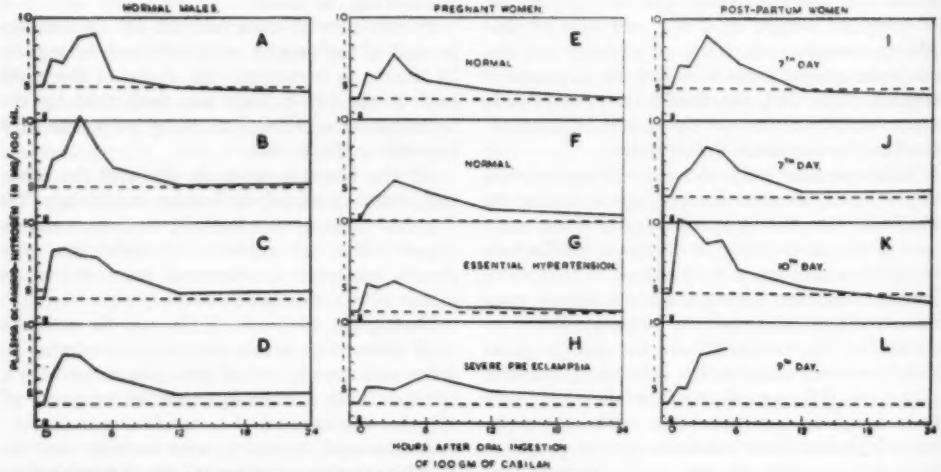

Fig. 1

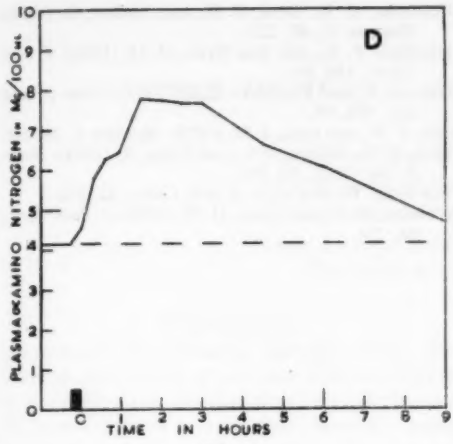

FIG. 2

was only 20·1 mg., but if this were directly injected into a plasma volume of 3 litres, and none were taken up by the liver or body tissues, it could theoretically cause a rise of 0·67 mg./100 ml.

As, however, the free amino-acids represented only 0·14 per cent of the amino-acids in the whole meal, and, as they certainly would enter the liver and the tissues, it is most improbable that this is the true explanation.

Intermittent gastric emptying might play a part in the production of these biphasic curves, but the relative constancy of their shape makes it more probable that the true explanation lies in the differing rates of absorption of amino-acids.

Seth and Luck (1925) estimated blood amino-nitrogen levels in rabbits following oral ingestion of equivalent amounts of various amino-acids, and showed that the maximal blood levels were reached at differing times for different amino-acids.

While the shape of the plasma amino-acid curves needs explanation, we have not investigated it further as it is not peculiar to pregnancy.

Although it is impossible to be certain from so few cases, the shape of the pregnant curve does not appear to differ essentially from the non-pregnant one; it can only be said that the pregnant curve starting lower does not reach so high a level.

One patient deserves special mention. She was a woman in the 30th week of pregnancy with severe pre-eclampsia and epigastric discomfort. During the 24 hours of the test she lost 9·4 g. of protein in her urine. The curve obtained is interesting, firstly, because it is clearly biphasic, secondly, in that the 3-hour peak was delayed till 6 hours, and, thirdly, because the maximal rise was less than normal. This may represent a delayed gastric emptying comparable to that found by Whiteley and Green (1952) in rats following muscle ischaemia. A study of many more patients will be needed to elucidate this matter.

SUMMARY

(1) Analysis of random blood samples from pregnant and non-pregnant subjects confirms the findings of Bonsnes, that the plasma amino-acid level of pregnant women is lower than normal.

(2) After oral ingestion of 100 g. of calcium caseinate, the plasma amino-acid level rises to a maximum at about 3 hours and falls more slowly, returning to its original level about 12 hours after the test meal. Sometimes there is a minor additional peak at half an hour giving the curve a biphasic appearance.

(3) The few curves so far obtained in pregnant women are similar in form to those of non-pregnant subjects, but starting lower they do not reach so high a level.

(4) A case of severe pre-eclampsia with epigastric discomfort showed a considerably delayed amino-acid curve.

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THE TECHNIQUE OF BREECH DELIVERY*

BY

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INTRODUCTION

ALTHOUGH any obstetric operation when performed successfully is a source of satisfaction to the operator, the one that gives me most pleasure is breech delivery or extraction. Here is a prime example of obstetric art; judgment, patience and technique all playing their part. One must give careful consideration to each individual case, and try to predict the course of labour accurately; one observes the patient carefully to see if the prognosis is being vindicated, and, if it is in every detail, one derives very real pleasure from one's success.

It is not my purpose today to discuss the management of breech presentation; whether to perform cephalic version or not, and when to deliver the breech abdominally. Whatever his views may be on these aspects, and no matter how ardently he may practise cephalic version in his own practice, one hard fact remains, the professional obstetrician in the course of his life delivers many infants by the breech through the vagina. Many of these cases may be emergency, or consultation, or hospital cases and not those of his own practice. Hence a detailed discussion on the actual technique of delivery is of interest to us all.

There are many different methods of assisting nature to deliver the breech, and a few of those are straightforward in their principle, easy in their application, and safe in their result. The techniques for which I have the highest regard as being the safest, and which have in common some basic principles are those of Burns (1934) and Marshall (1934) of Liverpool, and Løvset (1937) of Bergen. With the Liverpool method I am the most familiar, having worked in that centre for four years. While there I had the honour of meeting Professor Løvset, and of discussing his method with him. When considering extraction of the breech one should also mention Potter (1922) of Buffalo, but with his teaching I have not had direct acquaintance.

I hope that I am not misquoting Professor Løvset when I say that he thinks that his method is easiest for the general practitioner to learn and to become reasonably proficient in its exercise. I think this is true. His method is a more active one than the present Marshall technique, and because of this a beginner feels happier; he is doing something, and at each stage of the delivery has a sense of achievement. For the professional obstetrician, however, I think the Marshall method is superior. There is less manipulation, hence the delivery appears more elegant to the onlooker, and, once the technique is mastered, there need be no hitch in the smooth rhythm of delivery.

THE RESULTS OF THE LIVERPOOL TECHNIQUE

Before proceeding to the description of the method in detail, let us recall its record. In 1950, before the North of England Obstetrical and Gynaecological Society the records of 2,098 consecutive cases of breech delivery were presented (Cox, 1950). Included were 1,004 cases of single pregnancy, uncomplicated by placenta praevia, pre-eclampsia or other serious obstetric disorder having a prejudicial effect on

* Presented at the Third Conference of Fellows and Members of the Royal College of Obstetricians and Gynaecologists, held in Melbourne on 26th and 27th August, 1954.

the foetal salvage. In addition to the 2,098 cases 125 Caesarean sections were performed for breech presentation. This series extending over 16 years included those infants delivered while Burns and Marshall were considering the problem of breech delivery, and the cases of the preliminary report (Marshall, 1934) were included. Overall, the foetal mortality attributed to breech delivery alone was less than 5 per cent. As the technique came into general use, and refinements took place over the years, it was observed that the foetal mortality was gradually declining. In the last 5-year period of that report (1944–1948), the foetal mortality in 374 cases was 3·21 per cent. The improvement is being maintained, and the mortality for 1949–1952 has reached the low level of 2·41 per cent (249 cases). These are unselected hospital statistics, and deliveries performed by Marshall and his colleagues of great experience are included. But also included are many cases delivered by house-surgeons, students, and pupil midwives, who were learning the technique at the beginning of their training. It is not unreasonable to expect that better results would be attained in an individual obstetrician's own practice. More than one resident obstetrician at the Liverpool Maternity Hospital has a large personal series with a foetal mortality of less than 1½ per cent. Operators using other techniques have recorded personal series with very small foetal mortalities (Tompkins, 1943; Greig, 1945; Ware, Winn and Schelin, 1947).

These are the qualifications of this method, a foetal salvage of 95 to 100 per cent according to the operator's experience.

The Liverpool Technique of Delivery in a Primigravida When the Legs are Extended

(1) *Labour*. The conduct of labour should not be different from that of a normal vertex presentation. The duration of labour is much the same, the uterine contractions are just as strong, and the patient's behaviour is similar. The usual sedatives appropriate to the particular case, either pethidine, morphine, or hyoscine or some combination of these, should be given when contractions occurring at 5-minute intervals are beginning to distress the patient and the cervix is dilated to admit 2 fingers. When full dilatation is near, additional pain relief is welcome, and the use of nitrous oxide and oxygen or air, or trilene, is useful until the delivery. The common complications of labour occur with breech presentation, and a vaginal examination should always be made when the membranes rupture in case there is prolapse of the cord. The delivery is conducted in the lithotomy position, and a catheter is passed and the bladder is emptied in every case.

(2) *When to begin delivery*. The exact timing of the case is the most important feature leading to a smooth and effortless delivery. Although in some cases the commencement is in no doubt, for example, when a multigravida delivers the child's buttocks by voluntary straining, yet, in most primigravidae and in many multigravidae with large infants, this beginning is the crucial point. If assistance is offered too soon, undue force is used in the extraction, while, if it is offered too late, uterine inertia or foetal asphyxia may supervene with their attendant risks.

The time to begin the delivery is when the foetal anus is on view at the height of a contraction. If an episiotomy is made at this moment, the foetal buttocks usually will be extruded spontaneously and the delivery begins. When the anus has not appeared however, no matter how large the episiotomy may be, no matter how strongly the uterus contracts, groin traction by the operator is necessary for delivery of the buttocks to begin.

The time taken to reach this optimum point is remarkably constant. The foetal anus comes on view just over an hour, and seldom as much as an hour and a half from the time of full dilatation of the cervix. This time has elapsed while the breech distends the perineum and stretches the soft tissues. At last, when the knees of the foetus are behind the symphysis and the buttocks through the bony outlet, lateral flexion of the foetal spine occurs and the breech "rounds the corner". The foetal buttocks which seemed to be driving through the mother's anus curve forwards and the vulval orifice opens widely. Further progress is usually slow, and to await the spontaneous relaxation or tearing of the mother's perineum might take another hour. There is nothing to be gained by waiting for this, in fact everything may be lost instead.

Naturally it may not be wise to wait for this optimum beginning. Foetal distress may occur, or some other complication may necessitate immediate delivery, which then must be by extraction under anaesthesia. But let me continue, first, with the normal case, and consider the variations later.

(3) *The episiotomy*. This should be made always in a primigravida, and in most multigravidae, unless the child is extruded spontaneously. There are two important reasons for this step, which far outweigh any feeling of superiority the attendant may feel when he succeeds without it. The self-evident reason is that more room is made available at the outlet for any manipulations. The other reason is that part of the pelvic curve is obliterated, and the necessary hanging downwards of the child at a later stage is made easy. In a normal case the episiotomy is made under local infiltration analgesia, so that the mother's voluntary effort can still help the delivery.

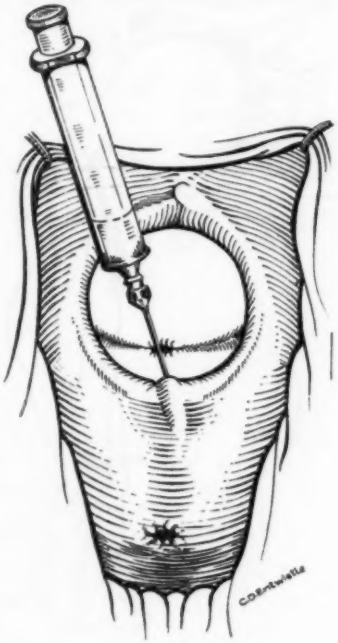

FIG. 1
Infiltration of local analgesic for the episiotomy.

(4) *The extrusion of buttocks, legs and body*. This stage is accomplished by the mother's voluntary effort. The attendant's finger may be inserted in the fold of the anterior groin to prevent the child from slipping back between expulsive efforts, but slight traction may be necessary in a normal case. One uterine contraction should be effective, but often a second contraction is needed to expel the buttocks. The buttocks rotate slightly, once they slip through the vulva, so that the sacrum, instead of remaining lateral in position, rotates anteriorly or posteriorly a few degrees.

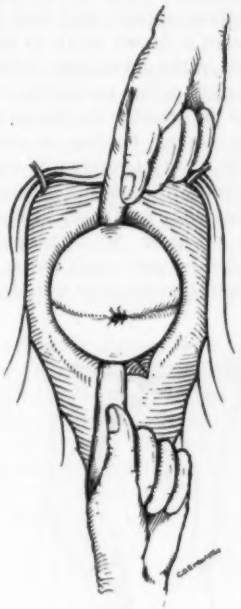

FIG. 2
Groin traction to aid delivery of the buttocks.

Now is the time for the operator to assume complete control. The mother's voluntary effort is complete, and anaesthesia is induced with intravenous thiopentone when the buttocks have been delivered. This method avoids straining and struggling by the patient which may occur if slower acting inhalation agents are used.

When the uterus is contracting very strongly the buttocks, legs, and body of the child are delivered spontaneously, but otherwise the operator needs to free the legs to allow the body to slip through the vulva more easily. The thighs are abducted and the knees flexed so that the legs and feet are freed. Now the legs hang down, and tend to rotate the body so that the sacrum becomes anterior.

The umbilicus appears and with it a loop of cord. The cord is drawn down so that it cannot become tight in the subsequent delivery, but no attempt is made to feel pulsations. It should be realized that the presence or absence of pulsation in the cord has no bearing on one's plan of campaign. It is very tempting, if one feels only weak pulsations, to hasten the remainder of the delivery. This is the very thing to avoid, a feeling of urgency or haste. So often pulsations are difficult to feel because one's hands are slippery with lubricant, that an error is easily made. It is far better to ignore the cord, and proceed with the delivery.

(5) *Freeing the thorax and arms.* The operator now grasps the ankles of the child. A sterile cloth prevents his grip from slipping. At this stage the child may make respiratory efforts. This should not cause alarm. The child's mouth is pressed firmly on the walls of the genital tract and inhalation of mucus and liquor does not seem to occur. The wrapping of the body of the child in warm towels is not a part of this technique, because it wastes time and confuses the operator's actions.

Grasping the ankles firmly, and, keeping the shoulders of the child in the sagittal plane of the mother, traction is made towards the floor. The thorax is pulled through the vulva, and at last the angle of the anterior scapula is visible. By holding the ankles in this way, trauma to the body of the child is avoided. Even the most

FIG. 3
Traction downwards.

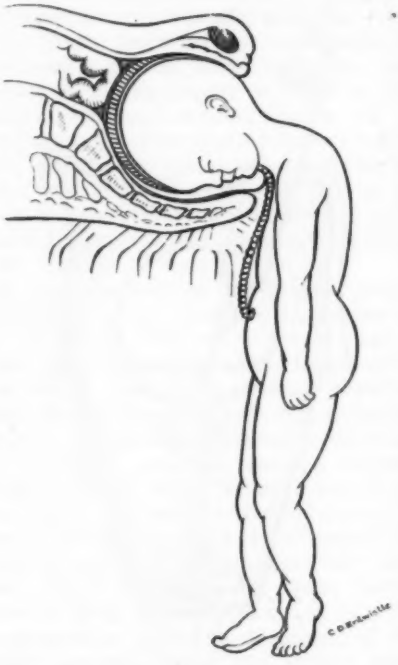

FIG. 4
The child hanging down.

rough handling would be unlikely to do more than break a fibula, in contradistinction to the abdominal injuries which can occur when the body is held roughly. At the moment when the scapula appears the anterior arm is partly extended. It is freed by feeling the acromion with the finger tip, running the finger up the humerus to the elbow, and dislodging this downwards. There is no risk of nuchal arm displacement provided the traction on the body has been downwards all the time, and rotation of the shoulders has been prevented. When the anterior arm is free, the body rotates, back uppermost, and the posterior arm, if not freed spontaneously, is dislodged, again by one or two fingers. The body now hangs downwards, suspended by the neck. The head is entering the pelvis, the sagittal suture in the transverse diameter and the biparietal diameter just within the brim.

As the body hangs, the head descends and rotates so that the occiput is behind the symphysis. Further descent with flexion occurs until the nape of the neck is clearly visible at the vulva.

(6) *Delivery of the head.* When the head does not descend completely in the pelvis, supra-pubic pressure by the operator himself, using the flat of his hand, is necessary. In this position, leaning forwards over the vulva, he is at a great mechanical disadvantage so cannot use great force, and will do no harm to the foetal head. Traction on the ankles towards the floor will help as well.

Grasping the ankles the operator swings them through a wide arc, maintaining tension, until the body of the child is over the vulva. This action pulls on the head, and, using the lower border of the symphysis pubis as a fulcrum, the foetal occiput pressing against it, the head rotates through the outlet so that the mouth and chin appear at the vulva. When the mouth is seen, the air passages can be cleared and respiration begins, although the head is not delivered.

(7) *Completing the delivery with forceps.* The foetal head may remain in the vagina for many minutes, and it is still important not to hurry the delivery. Sudden release of pressure may change the intracranial tension and trauma to brain substance occur. By applying forceps carefully the head may be extracted slowly, and sudden distortion prevented. Piper's forceps were

FIG. 5
The body swung upwards.

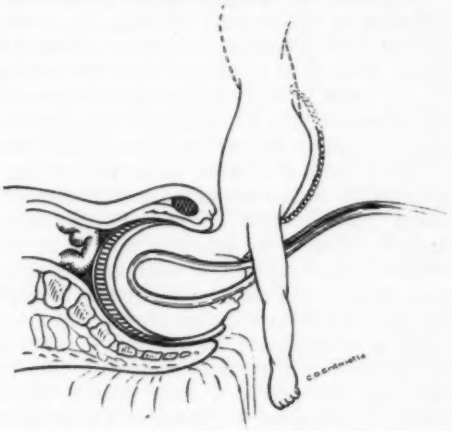

FIG. 6
Forceps applied to the aftercoming head.

designed for this extraction, but Simpson's or Neville's will do almost as well. It should be noted that the forceps are only applied when the face is visible, that is, the equivalent of a simple low forceps operation when the vertex is presenting. To apply forceps when the head is still in the pelvic brim, and to drag it through the pelvis is not recommended. It is much safer for the operator himself to apply suprapubic pressure to aid the descent of the head, than it is for him to apply forceps too soon.

(8) *Delivery of the placenta and repair of the episiotomy*. When the head is safely grasped with forceps, an intravenous injection of ergometrine 1·0 mg. is given. This causes a powerful uterine contraction which separates the placenta and allows retraction of the upper segment. The placenta is expelled and the episiotomy is repaired.

Important Variations of the Technique

The description I have given in detail is that for a primigravida when the legs are extended. There are many variations in the progress of labour when the breech presents, just as there are variations when the head does, and to describe each in detail would lengthen this paper to a monograph. Brief mention will be given of some more important types of case.

(1) *Flexed legs*. Broadly speaking there is no difference in the progress of labour, or in the delivery itself, if both legs are flexed and the full breech presents as a compact unit. The second stage is about the same length, but the phase of the delivery of the buttocks is a little quicker when the legs are flexed. When the breech is not complete and one member, either foot or knee, precedes the main mass of the breech, then the labour may become complicated. Whatever happens, whether the labour is delayed by the irregular presenting part, or whether it proceeds more rapidly with the limb protruding through the partly dilated cervix, there are two important warnings to remember. Be sure that the cord is not involved with the presenting part, and be sure that the cervix is fully dilated before delivery is attempted. To be sure of both of these facts, a number of vaginal examinations may be necessary, but there is no other way of gaining the information. Particularly with a footling presentation, the leg may protrude from the vulva and the cervix still may not be fully dilated. The patient in these circumstances usually bears down vigorously, but at all costs delivery must be delayed until full dilatation is reached.

(2) *Prematurity*. There should be no lessening of care when the child is small. Each step is more important than ever. The episiotomy allows extraction without any pressure on the soft foetal tissues, and a pair of small obstetric forceps, such as those of Wrigley, will protect the aftercoming head from trauma during its extraction. Often with a very small child (2–3 pounds) the perineum does not become distended at all, and one has to perform extraction under full anaesthesia or delivery would be greatly delayed. But if this is done gently and before foetal distress has appeared, the results are improved rather than worsened.

(3) *The large infant*. Labour is prolonged, and the breech does not descend into the pelvis. It remains high until the cervix is nearly fully dilated, and only then descent occurs. Such a case is fraught with peril, and is best handled by extraction under deep anaesthesia about an hour after full dilatation. One might intervene sooner, but a spontaneous delivery will sometimes occur after a normal second stage of about an hour. One should not delay intervention beyond that time because, when the breech becomes impacted just below the ischial spines, the uterus soon contracts around the child. The introduction of the operator's hand into the tightly stretched uterus may rupture the lower segment, for even under deep anaesthesia there may be little relaxation of uterine tone if there has been much delay. These cases are difficult, and should occur infrequently. The attendant always has warning of his difficulties during the first stage, and has time to consider the problem carefully, and he will solve it in many cases by Caesarean section. I will not dwell on this point, for it has been shown previously (Cox, 1950; Redman, 1950) that the foetal mortality in cases where the infant is large is very high.

(4) *Variations in technique due to the pelvic shape*. The technique described is applicable to the normal gynaecoid pelvis and the anthropoid

pelvis. The sagittal suture is in the transverse diameter as the head enters the pelvic brim and rotation of the foetal head occurs before it descends through the pelvis. When there is a flat or small gynaecoid brim it is important not to rotate the body after delivery of the anterior shoulder, to ensure that the head enters the brim with the sagittal suture in the transverse diameter and remains thus while it descends, rotation only occurring on the pelvic floor. This is accomplished by keeping the shoulders in the sagittal plane until the posterior arm is delivered, and only then allowing the back to rotate uppermost when the body is hanging by the neck waiting for descent of the head.

(5) *Extraction under anaesthesia.* When this is required, whatever may be the reason, the operator should not introduce a hand into the uterus until the anaesthetic has reached the necessary depth. Then with his palm against the foetal legs he gently advances his hand until the finger tips reach both feet, when flexion of the fingers causes flexion of the foetal legs. Both feet are grasped, and are withdrawn together. If for some reason both feet are not accessible the anterior leg is the one to be preferred. Both legs or one leg are withdrawn and traction on the ankles is begun just as in an ordinary delivery. There will be no alteration in procedure from this stage onwards, and extended or nuchal arms will not occur.

Labour

Having dealt with the delivery in detail, now we must consider the events leading up to the delivery. As I have already stated, labour proceeds almost exactly as it does when the head presents, and the same complications occur.

(1) *Incoordinate uterine action* or inertia may be present, and the foetal outlook is rendered grave. This complication is the worst that can happen from the mechanical point of view in any presentation, breech or vertex, but it is much worse when the breech presents. Very often in these cases, when the uterus is contracting abnormally, the foetus shows evidence of distress on the second or third day of labour, and one feels that delay in delivery will be fatal. If the head is presenting, and the cervix is nearly fully dilated, one might occasionally justify the digital stretching of the os, and the subsequent delivery with forceps; and certainly when the biparietal diameter is just within the rim of a fully dilated cervix it is no crime to apply forceps and deliver the child. But in such cases if the breech presents, even the most experienced and skilful operator will not achieve success in more than a proportion of cases. The cervix, which appears fully dilated in such a case, may contract about the shoulders or even the neck, and extraction is delayed and the child asphyxiated. It is safe to say that in breech presentation, if the operator is in doubt of the cervical dilatation, it is still incomplete, and vaginal delivery is unsafe. Only when the cervix has been completely dilated and when it has been drawn up during the retraction of the second stage is one free from worry on this score. Thus one can say emphatically: if there is abnormal uterine action, in most cases Caesarean section must be the method of delivery.

(2) *Foetal distress.* The appearance of this complication demands greater attention than in a cephalic presentation. For obvious mechanical reasons compression of the cord occurs for a longer time in the act of delivery of the breech than it does when the head is presenting. Normally an infant delivered as a breech suffers a little anoxia. If, due to the stresses of labour, the foetus is already partly anoxic when delivery begins, it is easy to see that asphyxia may develop before the delivery is finished. In these circumstances the operator sails between Scylla and Charybdis. If he pursues the unhurried rhythm of delivery asphyxia follows, while, if he hastens his actions, the aftercoming head may be suddenly deformed, and suffers cerebral trauma which proves fatal. The only escape is to set another course, to intervene at the first sign of foetal distress, before anoxia is present to any serious degree; thus one should extract the infant under full anaesthesia if the second stage is reached, or one should deliver abdominally without temporizing, if it is not.

(3) *Prolapse of the cord.* When the breech presents, this complication deserves no worse treatment than in a cephalic presentation. One is inclined to think that the breech does not fill the pelvis so that the cord will not be compressed and that the placental circulation will not be stopped. In most cases there is impairment of the

umbilical flow, so that foetal distress eventually occurs with its grave import for the breech. Whatever the presentation, breech or vertex, the discovery of a prolapsed cord should be followed immediately by delivery of the child by whatever method appears safest.

Antenatal Assessment

(1) *Cephalic version.* I do not propose to discuss this aspect at all. Although, because of the great interest shown there in breech delivery, the Liverpool school has never been a strong protagonist of cephalic version, it is not true to say that in Liverpool cephalic version is not performed. External cephalic version is performed in suitable cases where the risk to the foetus of version appears minimal, and where the version can be accomplished without difficulty. In other cases, where it is judged that a version is undesirable, or where the breech is already deep in the pelvis and version would almost certainly not be accomplished, version is not attempted and the breech presentation is allowed to persist.

(2) *Induction of labour.* When there is a large infant, and version is undesirable, or if it has failed, the obstetrician must consider his case further. Both Redman (1950) and Cox (1950) have shown the greatly increased risk of delivering a large infant as a breech. To avoid this increased foetal mortality one may either induce labour early to prevent the growth of the infant, or deliver by Caesarean section. Induction of labour at the 37th week has impressed me in certain cases, but one is hesitant to suggest it as a routine measure. Mair (1953) has reported a series of cases favouring this method. The case is assessed before term, and if suitable, labour is induced about the 38th week. There are important contra-indications to this method, particularly the flexed breech or the footling presentation when the presenting part is not engaged.

(3) *Caesarean section.* Cases of contracted pelvis and disproportion require section just as in a vertex presentation. Elderly primigravidae and patients with previous obstetric tragedies are those whose cases warrant Caesarean section although disproportion is not present. To attempt breech delivery in such cases is almost foolhardy. Abnormal foetal attitudes due to tumours and congenital anomalies of the mother are candidates for section, but simple extension attitudes of the foetus are not. Deacon (1950), Hall (1952) and Reis and DeCosta (1950) reported cases where vaginal delivery was accomplished without difficulty.

(4) "*Trial of Labour.*" The case that is difficult to assess is one with a mildly contracted pelvis and a normal sized foetus, in which, with the vertex presenting, one would allow a trial of labour without hesitation, knowing that with adequate uterine contractions vaginal delivery would be likely. The tendency with many authors is to state categorically that a trial of labour is impossible in a breech presentation. That is true if one accepts the old definition of a trial of labour, which lasts until the cervix has been fully dilated and the membranes ruptured for 2 hours. In these circumstances the breech becomes so firmly impacted in the pelvis that extraction vaginally or abdominally is fraught with danger. But a trial of labour in the modern sense, where progress is assessed after some hours of strong uterine contractions, is quite reasonable. If the breech engages the pelvic brim, the cervix dilates rapidly, and full dilatation occurs within the normal duration of labour, the outcome will be favourable. On the other hand, if the breech remains high in spite of strong contractions, and if the labour is obviously lasting longer than normal, then disproportion exists, and abdominal delivery is necessary if good foetal results are to be maintained.

Conclusion

There is much more that could be said about this subject, and there is much more that I should like to say, but the time allowed for the discussion does not permit. You will observe that the title of this paper is "The Technique of Breech Delivery", and that I have confined my description to the modern version of that described by Burns and Marshall. This technique, now over 20 years old, can be said to have proved itself to the satisfaction of its authors. It has proved itself by its results, and its value as a piece of obstetric art is shown by the fact that those who use it enjoy practising it.

No person however talented can achieve

perfection in any aspect of his work except after practice and precept. This is particularly true of breech delivery. One must be trained in a method, then must practise it. In this matter the training of the professional obstetrician breaks down in many schools. Breech presentations occur infrequently, and, because it is thought to be good practice to perform cephalic version, many of us make the presentation a rarity. There is no doubt, however, that, while the general practitioner may plan to avoid breech deliveries, the obstetrician cannot, however he may conduct his own practice. Therefore I make this plea: In every teaching school, let more and more emphasis be placed on the art and technique of breech delivery. Even if it becomes a more common procedure, the results in the long run will be improved. The obstetrician-in-training, if well supervised, is not very likely to increase the foetal mortality with a breech delivery, and, if he has been trained carefully, he will approach the problem in the future with a new confidence, and eventually will take pleasure in his art.

Summary

(1) The results of breech delivery at the Liverpool Maternity Hospital are recorded.

(2) For the last 4 years, 1949–1952, the foetal mortality in 249 cases was 2·41 per cent (Table I).

(3) The Liverpool technique of delivery is described in detail.

(4) It is suggested that in teaching hospitals where there is an emphasis on post-graduate obstetric training the foetal mortality will not be increased if fewer cephalic versions and more breech deliveries are performed.

Table I

Liverpool Maternity Hospital
Foetal Mortality in Uncomplicated Breech Delivery

Years	Cases	Foetal Mortality Per cent
1933–1938	318	7·23
1939–1943	312	4·80
1944–1948	374	3·21
1949–1952	249	2·41

Acknowledgment

I am most grateful to the Medical Staff of the Liverpool Maternity Hospital for permission to use previously published statistics, and for supplying the recent figures for 1951 and 1952, which are still in course of publication.

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THE DIAGNOSIS OF PELVIC TUBERCULOSIS*

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I HAVE been interested in tuberculosis of the female genitalia for the last 7 years. During this time I have personally looked after 30 patients with this disease. Most of these were admitted to hospital because of an acute gynaecological condition. Four came from the Fertility Clinic at the Women's Hospital, Melbourne, in 2 of which the diagnosis of tuberculous endometritis was made on histological examination of the endometrium. The other 2 cases were diagnosed later, 1 when a plastic operation was about to be done on the tubes, and the other during an attack of acute salpingitis following endometrial biopsy.

In the last 18 months at the Fertility Clinic at the Women's Hospital 3 cases of tuberculous endometritis were diagnosed in 430 new patients, an incidence of 1 in 143. I do not propose to discuss in this paper the problem of the patient who is attending a Sterility Clinic and in whom a diagnosis of tuberculous endometritis is made from an endometrial biopsy.

I propose to discuss one aspect of pelvic tuberculosis, namely, its diagnosis. I have chosen this aspect because I consider the diagnosis of the condition particularly difficult. Of the 30 cases under discussion, the provisional diagnosis on admission to hospital is shown in Table I.

In only 1 case was a correct provisional diagnosis made and this was in a patient who had had tuberculous meningitis previously and who presented as a definite general peritonitis.

General or pelvic peritonitis was diagnosed in 8 cases and acute salpingitis in 7 cases. In the remaining 15 cases several provisional diagnoses were made.

TABLE I

Provisional Diagnosis

Pelvic or general peritonitis	8
Acute salpingitis	7
Sterility for investigation	4
Ectopic pregnancy	3
Fibromyomata uteri	3
Menorrhagia for investigation	2
Ovarian cystomata	1
Missed abortion	1
Tuberculous peritonitis	1

I shall discuss the problem of the diagnosis of pelvic tuberculosis under the following headings: (1) age incidence, (2) symptoms of the disease, (3) signs of the disease, (4) histological diagnosis, (5) bacteriological diagnosis, (6) X-ray diagnosis.

TABLE II

Age		Per cent
10–20	1 case	3
20–30	19 cases	63
30–40	4 cases	13
40–	6 cases	20
	30 cases	

AGE INCIDENCE

This is a disease of young people: in this small series most were in the age group 20–30, with a few before 20 and a few after 30. Six cases occurred in people over 40. It is therefore important to remember that this disease can occur in older patients.

* Presented at the Third Conference of Fellows and Members of the Royal College of Obstetricians and Gynaecologists, held in Melbourne on 26th and 27th August, 1954.

TABLE III
Fertility

Previous children	4 cases
Previous abortions	4 cases
Previous ectopic	1 case
Total previous conceptions ..	9 cases (30 per cent)

SYMPTOMS

Fertility. The *infertility* of the patients with this disease is well known, and in the series no patient has had a baby since the diagnosis was established. However Table III shows that the reverse does not hold and that 4 patients had had a previous child, 4 had aborted and one had had an ectopic pregnancy. That is, 9 of the 30 patients conceived presumably before or soon after they were affected. At the initial visit 4 cases had amenorrhoea—of these 3 subsequently aborted and one had an ectopic pregnancy.

Although 12 of the patients complained of *sterility*, only 4 had been investigated for this prior to the diagnosis of tuberculosis. Menorrhagia occurred in 6 but was never of a severe degree. Four patients complained of dysmenorrhoea, and 3 had no symptoms at all.

Table IV is a summary of the symptoms that the patients complained of when they made their first visit to their doctor during this illness. The commonest symptom was lower abdominal pain —22 complained of this. The type of pain was usually continuous but not severe. The pain directed our attention to the pelvis as being the most likely situation of a pathological process. The amount of pain certainly varies with the activity of the disease and often determines whether treatment should be surgical or conservative.

To sum up, the patients usually complain of lower abdominal pain and some complain of sterility. The patients tend to be in poor general condition and are prone to fatigue. There is no clear clinical picture of the disease.

SIGNS OF THE DISEASE

Table V shows the incidence of the disease in the internal genitalia.

In 28 cases both Fallopian tubes were involved. The two types of tuberculous salpingitis which have been described were seen. In one type the tube is swollen considerably, the exterior is smooth with very fine adhesions making operative removal easy. On section the tubes are filled with caseous material.

In the second type the tube is usually obscured by dense adhesions to small bowel and surrounding structures, making surgical removal difficult. The tubes show only slight enlargement and often elongation; the enlargement may be irregular, giving the appearance of salpingitis isthmica nodosa.

Twenty-one cases showed involvement of the endometrium—a higher percentage than in most published reports. Some writers have made a feature of "sparing of the endometrium". This has not been my experience in this series. When the Fallopian tubes are affected, if evidence of tuberculous endometritis is sought, it will usually be found. Dilatation and curettage is the best method of doing this. On vaginal examination there was enlargement of the uterus in only 2 cases. In one it was due to the presence of several fibromyomata and in the other to an adenomyoma of the uterus. When the latter was removed it was found that the adenomyoma was the seat of extensive caseation, the tuberculous process having invaded the area from the endometrium (Fig. 1).

If the patient is in the child-bearing period, prior to menstruation the endometrium will appear normal on visual examination. One patient, who had ceased to menstruate 10 years

TABLE IV
Symptoms at First Visit
(Percentages in brackets)

None	Sterility	Abdominal Pain	Amenorrhoea	Menorrhagia	Dysmenorrhoea
2 (10)	12 (40)	22 (73)	4 (13)	6 (20)	4 (13)

TABLE V

Frequency of Site Affected
No. of Cases—30
(Percentages in brackets)

Site	No. of Cases	
Fallopian tubes	28	(93)
Uterus	21	(70)
Peritoneal cavity	17	(57)
Ovaries	6	(20)
Cervix	1	(3)
Vagina	1	(3)

previously, had numerous small yellow shallow ulcers scattered all over the inner surface of the uterus, indicating extensive involvement of the endometrium.

In 17 cases the tuberculous process involved the pelvic or general peritoneal cavity. Two types of peritonitis are seen. In the commoner variety, grey-white tubercles are seen covering the parietal and visceral peritoneum. In some cases the tubercles are confined to the pelvis, covering the uterus, rectum and bladder, while in others the general peritoneal cavity is affected. In the latter type the tuberculous process is superficial and does not involve the viscus underneath the peritoneum. There is usually some straw-coloured fluid in the peritoneal cavity.

A rarer type of peritonitis may also be seen in which there is a more extensive involvement of the peritoneal cavity. Here the pelvic organs are obscured by a process which matts the large omentum, small bowel, and pelvic organs together. The adhesions are very tough and operative removal is extremely difficult.

In 6 cases the ovaries were involved secondary to the process in the Fallopian tubes, i.e., a perioöphoritis. No case was seen where a blood-borne infection of the ovary had produced an oöphoritis.

The cervix and vagina were involved in 1 case. A large ulcer involved both the cervix and vagina and biopsy proved the diagnosis (Fig. 2). Healing took place during a course of streptomycin and P.A.S. (Fig. 3).

It is agreed that pelvic tuberculosis is most commonly secondary to a primary process in the lung. It is probable that in the female the disease starts in one of two ways:

(1) There is a blood-borne spread to the Fallopian tube from whence it spreads to the endometrium or the ovary and the pelvic peritoneum. In this type the patient presents with acute salpingitis.

(2) There is a simultaneous blood-borne infection of the pelvic organs and the general peritoneal cavity. The patient presents with general or pelvic peritonitis, sometimes associated with acute salpingitis.

TABLE VI

Physical Signs on First Examination
(Percentages in brackets)

Signs	No. of Cases	
Mass in pelvis	22	(73)
Peritonitis or pelvic abscess	17	(56)
Pregnancy	4	(13)
None	6	(20)

Twenty-two cases on pelvic examination had palpable masses situated outside the uterus. There was nothing characteristic of these masses to suggest the tuberculous nature of the salpingitis. On abdominal examination 17 patients had signs of general or pelvic peritonitis. Four had signs of early or recent pregnancy and 6 were normal on both pelvic and abdominal examinations.

In all but the 1 case mentioned previously the tuberculous nature of the peritonitis or salpingitis was not appreciated at the first examination.

HISTOLOGICAL DIAGNOSIS

Endometrium. In many cases histological examination of the endometrium gave the initial diagnosis of tuberculosis. This was particularly so in cases where a laparotomy had not been done. In this series 70 per cent of the cases had tuberculous endometritis diagnosed by histological examination. In 12 patients the first positive specimen was obtained by curettage and in the other 9 by endometrial biopsy. If tuberculous endometritis is suspected a dilatation and curettage of the uterus should be done; an endometrial biopsy is not an adequate method of investigation. Once a diagnosis is made, further

curettages should be done at infrequent intervals for reasons that will be noted later.

Tubercles with caseation are rarely seen on microscopic examination of the endometrium because in menstruating patients the endometrium is shed before such a stage can be reached. Sections cut from endometrium in the first 3 weeks of the cycle show only early tubercles, i.e., epithelioid cells and small round cells (Fig. 4). However, just before the period is due, typical tubercles may be seen with the usual characteristics, giant cells, epithelioid cells and small round cells (Fig. 5). Gray (1951) has shown that the bacilli may be demonstrated in these areas by fluorescent microscopy.

In some cases the number of tubercles seen in one block is scanty and has to be carefully looked for. Extensive caseation in the uterus is only seen in post-menopausal cases and when the disease occurs in an adenomyoma.

When investigating a case in which a laparotomy has not been done, if the endometrium is tuberculous as proved by histological examination, it is reasonable to assume that any adnexal masses palpable are also tuberculous. In all cases that have been subsequently treated surgically in which this has been done, the tubes have been found to be tuberculous.

Although the tubes were affected clinically in 28 of the patients, histological examination provided the initial diagnosis of tuberculous salpingitis in only 5 patients. In the 12 patients in whom the tubes were removed, all the tubes were affected with tuberculosis when examined histologically.

Fallopian Tubes. The histological picture when the Fallopian tubes are affected in the acute phase is typical of tuberculosis elsewhere in the body. Caseation may or may not be present. When the disease has reached a chronic stage or healing has taken place, an adenomatous pattern is often seen in the rugae (Fig. 6). This may resemble an adenocarcinoma.

Inclusion bodies in tuberculous salpingitis have been described by Schaumann (1941), Potts (1951) and others. One type is an intracellular non-siliceous anistropic crystal and the other a concentric laminated iron-containing body. These may occur in or near tubercles in the tubes (Fig. 7).

Omentum. In 4 patients biopsy of the omentum was done, and after histological examination this was shown to be tuberculous and confirmed the diagnosis of a tuberculous peritonitis.

Bacteriological Diagnosis

Bacteriological proof is stated to be necessary before any lesion is declared to be tuberculous. This standard cannot always be attained. Usually the diagnosis of tuberculosis is made on histological examination and proof is sought by bacteriological examination.

In this series 10 patients were proved to be tuberculous by bacteriological examination; in 7 of the 10 the bacteriological report was the first positive finding in establishing the diagnosis, and in 3 of these it was the only positive finding which I was able to obtain.

Table VII

Bacteriological Findings

Source	Stain and Culture		Animal Inoculation	
	+ve	−ve	+ve	−ve
Cervical smear ..	6	9	0	0
Endometrium ..	1	7	2	2
Menstrual flow	2	3	0	0
Peritoneal fluid	6	0	6	0
Urine (24 hours)	3	6	3	6

This Table shows the various sources from which bacteriological proof was sought and the number of tests that were done. Cervical smears proved positive in 6 out of 15. Cultures of the endometrium proved disappointing; only 1 in 7 was positive. Culture of the peritoneal fluid or discharge from the sinus was successful in the 6 cases in which it was done. It is difficult to culture the menstrual flow. In 2 of the 5 patients in which it was performed it was positive. All sources may have to be investigated many times before a positive finding is obtained. It is important not to be deterred by one or two negative findings. Of the patients, in whom a 24-hours specimen of urine was examined, the bacillus was found in 3.

X-ray Diagnosis

I have had hysterosalpingograms taken in 7 of the 30 cases in this series. The findings agree with those of Magnusson (1947) and Madsen (1947) who stated that there are three main types of salpingogram in tuberculous salpingitis.

The first and common type occurred in 5 of the 7 cases. Here we see an even, elongated straight contour of the Fallopian tube with a pipe-like appearance, and blockage at its fimbriated end. The tube does not empty itself completely after 24 hours.

The second type occurred in 1 case. Here the whole Fallopian tube is dilated and we see a picture similar to any pyosalpinx. The picture is therefore not typical of tuberculosis. The hysterogram is of interest because after 24 hours there is some peritoneal spill. This is the only hysterogram showing tubal patency.

The third type occurred in 1 case. Here the tube shows a fine jagged and ragged contour, with small linear defects and little dilatation of the tube save at the fimbriated extremity. The tube is blocked at this end. In this patient there is also an extensive tuberculous endometritis.

Hysterosalpingogram is an aid to the diagnosis of tuberculous salpingitis. It will establish the presence of an inflammatory process and direct attention to the possibility that the inflammation is tuberculous. The common type of picture is not specific of the disease—it is suggestive only. The uncommon type is more definite, especially if the endometrium is involved. Calcification of the tube is very suggestive. No such case was found in this series.

These methods of diagnosis are not without danger. In this series 3 cases had a Rubin's test and 1 developed an acute attack of salpingitis following the test. Of the 15 endometrial biopsies that were done in this series 1 subsequently developed an acute salpingitis. There were no complications following the 20 curettages and none following 7 hysterosalpingograms; however all four methods of investigation have risks, and, although I think it is necessary to take risks in establishing the diagnosis, once it is made repeated tests to judge progress of treatment should only be done infrequently.

Table VIII

Final Diagnosis (First Positive Finding)

(Percentages in brackets)

Method	No. of Cases	
Histological examination of endometrium	14	(47)
Bacteriological examination	7	(23)
Histological examination of Fallopian tube	5	(17)
Histological examination of omentum ..	4	(13)

This Table shows the frequency with which each method of diagnosis gave the first positive finding in the patients under review. In 23 patients histological examination established the diagnosis; subsequently 7 of these had bacteriological proof. In the other 7 patients a positive bacteriological finding established the diagnosis and in 4 of these it was later confirmed by histological methods.

The diagnosis of pelvic tuberculosis is not easily established in the first instance, and when made by one method it is often difficult to confirm by another.

To sum up, if a case is suspected as being one of genital tuberculosis, we have found the following points important.

(1) A careful history must be obtained to ensure that any past evidence of tuberculous disease in the patient or her family is obtained.

(2) A past history of sterility or of pelvic inflammatory disease in a virgin is very suggestive of tuberculosis.

(3) A history of chronic lower abdominal pain and discomfort in a patient who is not feeling well and who is over-fatigued should arouse suspicion.

(4) Changes in the menstrual cycle have not assisted in the diagnosis.

(5) Acute pelvic disease, with or without peritonitis, should always arouse suspicion of tuberculosis especially if it does not respond to the usual chemotherapy.

In a suspected case the following examinations should be carried out.

(1) Histological examination of the endometrium after a dilatation and curettage.

(2) Biopsy of any suspicious areas of the cervix.

FIG. 1

FIG. 2

FIG. 3

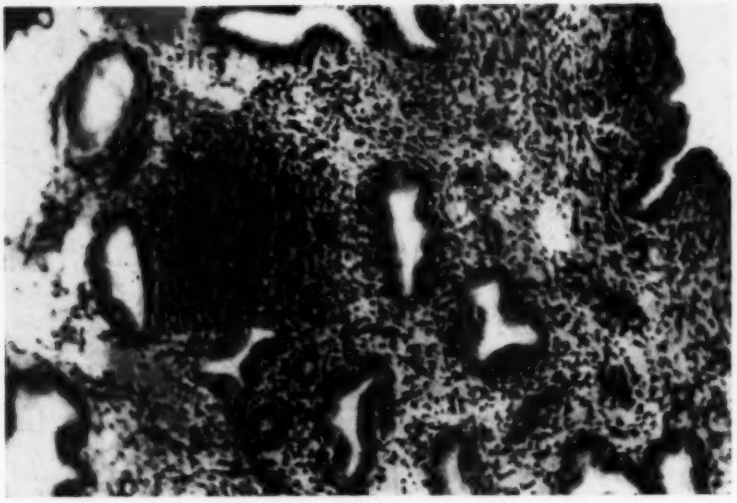

FIG. 4

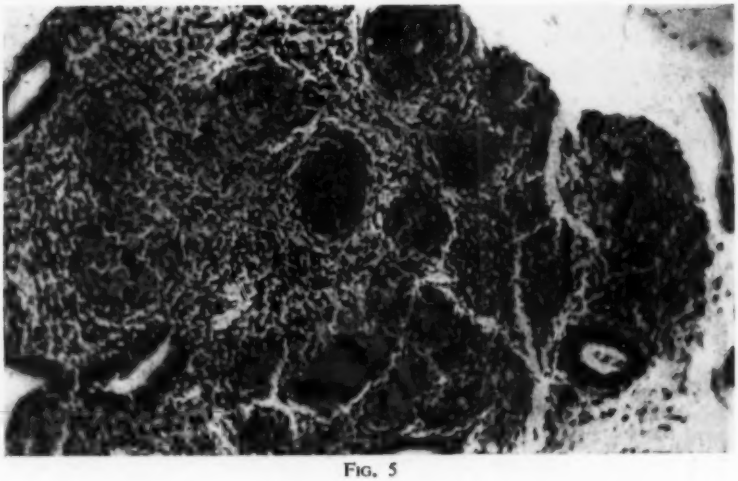

FIG. 5

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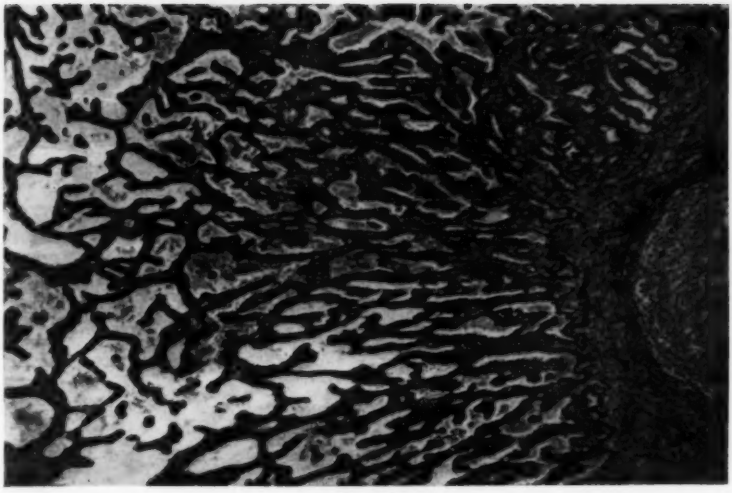

FIG. 6

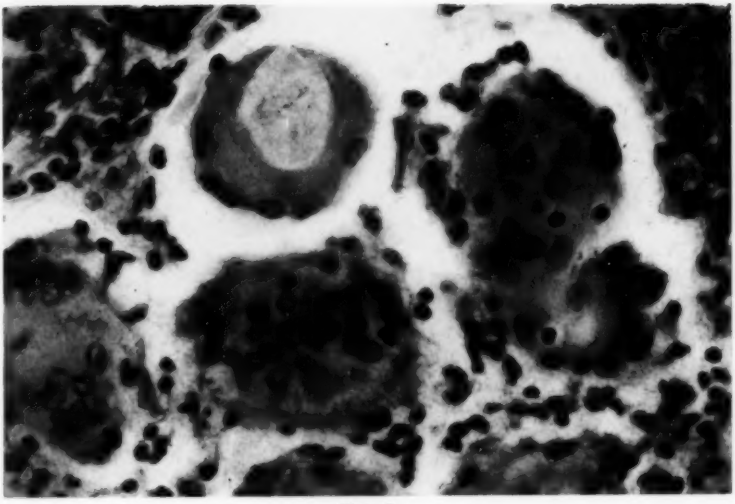

FIG. 7

(3) Bacteriological examination of the endometrium, of menstrual blood, of peritoneal fluid or discharge from abdominal or vaginal sinus.

(4) Hysterosalpingography.

When this complete routine is carried out, few cases of pelvic tuberculosis will escape diagnosis for any length of time.

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IMPLANTATION OF THE FALLOPIAN TUBES FOR STERILITY*

BY

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APPROXIMATELY one marriage in 10 proves to be sterile, and complete occlusion of the Fallopian tubes is found in our Clinic to account for one in 6 of these cases. This incidence of tubal blockade in one in 60 of all married women presents a challenge to gynaecologists, and this is made more acute by the frustration it produces in the patients, and their perseverance in search of relief. Softening-up treatments, using electrical heating and oestrogens, or repeated insufflations and injections to persuade the tubes to open, are often futile, and there remain many cases in which nothing short of reconstruction of a new pathway into the uterus can offer any hope. It has commonly been assumed that the best patients for surgery are those with blockage and dilatation at the fimbriated end, and in cases with localized blockage in the narrow part of the tube near the uterus, the prognosis is almost hopeless and operative reconstruction not worth attempting. This pessimistic view of operative intervention was consolidated by Greenhill (1937), who, in reply to a questionnaire, reported that the majority of American gynaecologists were opposed to operation of any type. There were only 36 live babies reported in 813 plastic operative procedures of all types, besides abortions and ectopic pregnancies; or one live baby in 22·5 operations. Greenhill (1953) still doubts whether the position is much improved.

A series of cases is described to give some contradiction to this opinion, and to illustrate points of technique which have been developed with time. Similar techniques and encouraging degrees of success have been described by Green-Armytage (1952), White (1951), Palmer (1952), and Swendson (1953). The technique is also described in the current American textbooks by Te Linde (1946), and Parsons and Ulfelder (1953).

PATHOLOGY

Cases in which the tubes are blocked can be put into three clinical groups:

(1) Tubes completely disorganized by inflammatory processes and unfit for operative reconstruction.

(2) Cases in which the tubes are blocked at the outer end, producing the familiar retort-shaped sactosalpinx. The peculiar thing is that when this condition is present the uterine end of the tube is almost invariably open. Cuff-salpingostomy however is rarely followed by pregnancy, because reclosure of the tube with peritoneal adhesions is common, the fimbriae and cilia are destroyed, and the tubal wall is stiff and not capable of peristaltic action.

(3) Tubes blocked over a localized area close to the uterine end, the remainder of the tube with its "egg-catching" fimbria being usually normal.

It is only this last type of case which is suitable for the operation of tubal implantation. The condition results often from a mild subclinical catarrhal inflammation following a normal labour or abortion, and it is a common type (Green-Armytage, 82 per cent). It has become more important since the use of antibiotics. In the past, these cases have been considered unsuitable for surgery, but there is a growing feeling amongst those associated with sterility clinics that this pessimism is unwarranted. Important factors in this change of attitude have been improved operative technique from the concentration of material in Fertility

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Clinics, the use of special instruments and procedures to preserve patency of the lumen, and a better appreciation of the physiology of the Fallopian tube.

Physiological Premises

It is a physiological principle that fistulae of tubular structures tend to close, and the essential continuity tends to be restored, provided there is no obstruction distally. The Müllerian duct is no exception, and because of its primitive embryological origin, and its biological importance in preserving the species, this propensity may be inherent to a more marked degree. The number of failures following operations for deliberate sterilization emphasizes this tendency. After hysterectomy, with no attempt at anastomosis, the cut medial ends of the tubes not uncommonly find their way into the corners of the vaginal vault, prolapse of the tubal mucosa may occur, and ectopic pregnancy has even been recorded in the tube in such cases.

Application of the usual techniques of surgical anastomosis is complicated by two factors; the smallness of the lumen of the Fallopian tube, especially in its medial half, and the thick condensation of muscle surrounding a slit-like cavity in the uterine segment. It is only in the lateral half or third that the tube has a lumen of a size which is capable of surgical manipulation. The procedure of election, therefore, is to circumvent the blockage, by implanting into the uterus the outer end of the shortened tube, thus preserving the important fimbriated end which attracts the egg across the tubo-ovarian hiatus, but relying on natural processes to restore the lumen into the uterus. This has been accomplished by reposing the cut ends of the tubes in the ends of a coronal incision made across the fundus (Berkeley and Bonney, 1942), or by introducing them by various means through a new artificial opening at the uterine angles. The interstitial tunnel has been made by forcible disruption of the muscular tissue, excision with a fine blade, or smooth coring with a trephine instrument. Such a procedure is distinct from the usual operations of salpingostomy and salpingolysis, and is a true anastomosis, although it lacks the finesse of technique such as that used in the intestinal tract, or implantation of the ureter into the bladder or colon.

Selection of Cases

In selecting cases the following points need emphasis:

(1) Tests for tubal patency must be adequate, including X-ray examinations. The liability of the tests to error, due to spasm in the important region under consideration, must be remembered. The contour of the uterine angles on X-ray examination should be sharp and pointed; rounding of the cornual angles suggests spasm. The small flask-like dilatations of the tube just distal to the sphincter area may stand up at the angles like two dog's ears, but if the radio-opaque fluid passes some distance down the tube the outlook is bad, and the tubes are usually disorganized over their remaining length.

(2) Genital tuberculosis should always be excluded as far as possible by at least one endometrial biopsy. In this condition portion of the tube showing a moth-eaten appearance is often outlined.

(3) Investigation must show the husband's fertility to be adequate.

(4) Fixity of the uterus, and the presence of adnexal masses are unfavourable, but palpation of a movable uterus and smooth mobile ovaries are hopeful signs. An antecedent pelvic infection of clinical degree is unfavourable, although a history of a normal pregnancy or abortion is often obtained.

(5) The possibility of an unsuccessful operation should not be minimized to the patient.

(6) It is preferable to operate after menstruation, rather than before it has occurred.

Operative Technique

The method first described was commenced seven years ago and used up till the end of 1952, but has been discarded in favour of what may be an improved technique.

(1) An armamentarium of some special instruments such as the following has been found necessary in dealing with such fine structures as the Fallopian tubes.

(*a*) Fine toothed dissecting forceps such as used in eye work.

(*b*) Fine scissors of eye type.
(*c*) Mosquito artery forceps.
(*d*) Long fine curved clamp of thyroidectomy type.
(*e*) Small sinus forceps.
(*f*) Leur-Lok ring-grip syringe, 10 or 20 ml., with glass plunger.
(*g*) Insufflation cannula, with olive tip and Leur-Lok fitting.
(*h*) Fine pointed scalpel.
(*i*) Atraumatic needles with OO chromic gut.

(2) The pelvic viscera are exposed, using Balfour's retractor in moderate Trendelenburg position. The operation is abandoned if the tubes are disorganized or appear tuberculous.

(3) Using the syringe and cannula, the tubes are insufflated from the fimbriated end which can be closed with the fingers round the bulbous end of the cannula, and the air can be visualized passing down the sinuous outline of the tube. Resistance is shown by the recoil of the smooth-sliding glass barrel. The gurgle of air into the uterus and vagina can usually be heard, but the passage is best tested by placing the pulp of a finger lightly on the uterus, when the crepitus is easily felt as the gas passes. Retrograde insufflation from the vagina with cannula *in situ* has not been used.

(4) Two strong silk guy-ropes, taking a good bite, are transfixed through the uterine fundus, leaving at least one cm. between them in the sagittal plane.

(5) A hole is made in the avascular part of the mesosalpinx, and enlarged, leaving sufficient web and blood supply laterally to supply the outer end of the tube. It is usually advisable to ligate a vessel close to the tube in the mesosalpinx on the lateral side.

(6) The open outer end of the tube is then prepared for implantation by clamping it medially where it has been separated from the mesosalpinx, and slitting it into anterior and posterior fish-mouth flaps by transfixation with a fine sharp-pointed wafer-blade scalpel, making each flap 5 mm. or a little longer. An alternative method is to slit the tube by cutting down on to a cannula passed down the lumen of the tube, or it may be split with fine scissors after the tube has been divided (Fig. 1, A).

(7) Each flap is transfixed with fine chromic gut on an atraumatic needle, and doubled back to take a second and firmer bite into the peritoneal coat to evert and spill out the tubal mucosa.

(8) The medial blocked portion of the tube is resected down and ligated close to the uterus, although this has been omitted in later cases. The opposite tube is then prepared in a similar manner.

(9) A sagittal incision is then made across the fundus between the guy-ropes exposing the endometrial cavity; a Bonney myomectomy clamp has been used but is not usually necessary.

(10) Using a curved rather sharp haemostatic forceps passed from the endometrial cavity in the cornual region, a hole is forced through the uterus and enlarged to the appropriate size by opening the forceps. The hole is usually just behind the tubal insertion (Fig. 1, B).

(11) The transfixing sutures on the tubal end are drawn through the opening into the uterine cavity on mosquito forceps, and the tube then led into the cavity by even traction. This is the most difficult part of the operation. Assistance can be given by sliding the tube in over a probe, or using a curved cannula passed down its lumen, to serve as a guide or internal splint. The long fine curved forceps may be passed through the opening from the inside of the uterus, taking a firm grasp of the mesosalpinx close to the tube, to assist in the manœuvre.

(12) The traction sutures are then separately threaded on to a needle and the uterine substance transfixed from within out so as to emerge on the cut sagittal surface of the uterus, where they are tied, thus placing the flaps towards the back and front of the uterus.

(13) A few fine sutures are placed round the tubal insertion, holding the peritoneal coat of the tube to the uterus round the artificial opening, and the mesosalpinx is then lightly sutured to obliterate any gap. Air can then be blown down the shortened tube to appear as bubbles in the uterine cavity (Fig. 1, C).

(14) When both tubes are implanted the sagittal incision in the uterus is closed, and the silk guy ropes removed.

(15) Chemotherapy is given after the operation, but it is advisable not to insufflate or inject the tubes for at least six months.

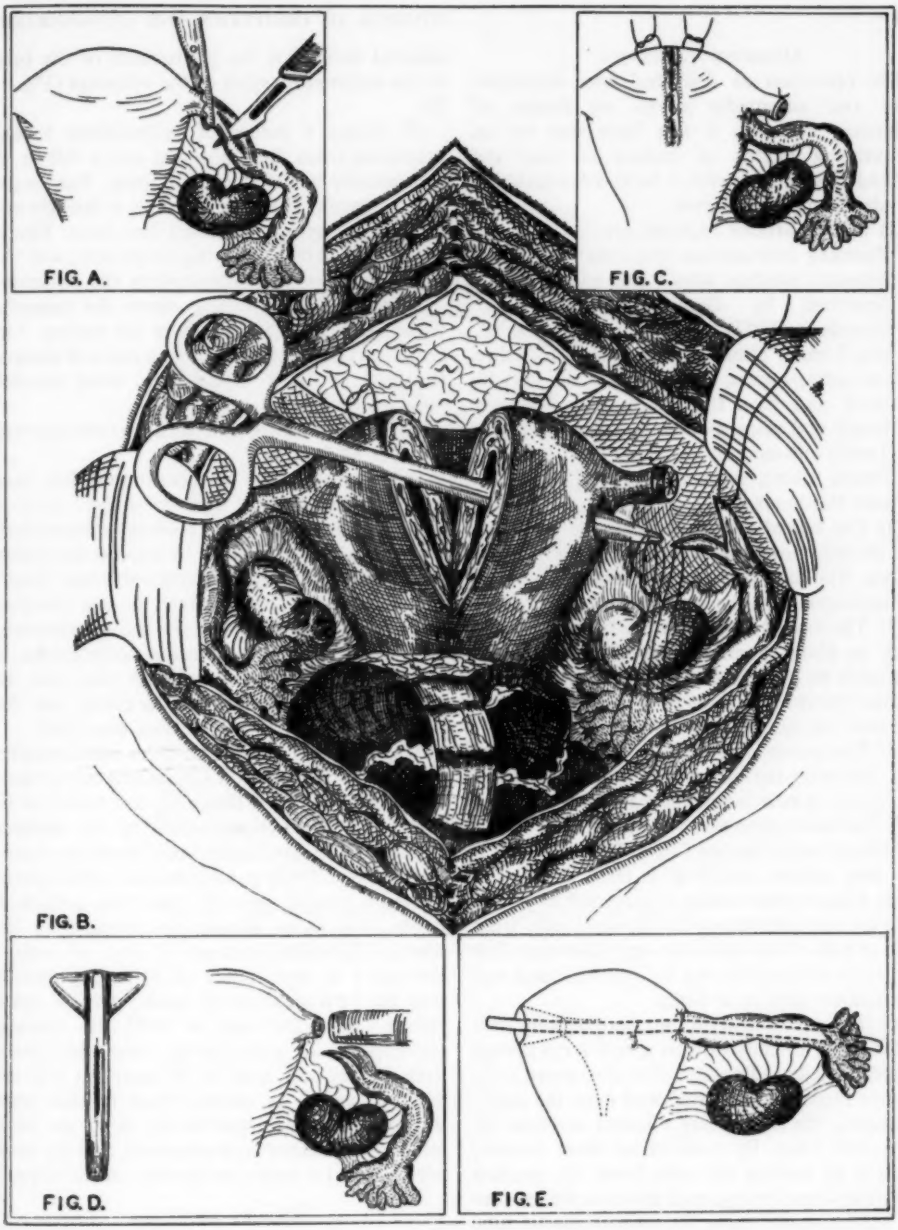

FIG. 1

Stages in tubal implantation. A—method of fashioning fish-mouth flaps by transfixing the tube. B—withdrawing the guy sutures through an opening made by forcible disruption with forceps from a sagittal split. C—the tube anchored *in situ*. D—Silcock's punch used in the reaming method without splitting the uterus. E—shortened tube implanted over polythene tube.

Modified Technique

The operation as described was developed early and admittedly shows no finesse of technique, although it has been met by an encouraging degree of success so that the method has been modified to avoid mutilating the uterus to such a degree.

(1) Special articles required are:

(*a*) Reaming instruments, the ones used being Silcock's punches, sizes 7 mm. and 9 mm., as described by Green-Armytage (1952). Swendson (1953) uses a corneal trephine, size 5 mm., although domestic instruments for coring-apples, and boring corks may be used, and have the advantages of greater length and being made in graduated sizes.

(*b*) Trocar and cannula.

(*c*) Plastic tubing, size 2 and 3 Polythene (Allen and Hanburys Ltd.).

(2) The lateral end of each tube is prepared, and the fish-mouth flaps held long on sutures as before. The silk guy-ropes through the uterus are unnecessary as the uterus is not split.

(3) The medial portion of the tube is resected back to about 5 mm. from the uterus. It is advisable to ligate the recurrent branch of the uterine artery in a transfixing suture, taking a bite into the uterus just below the tubal angle.

(4) The punch is placed over the tubal stump, and, following the line of the tube in its interstitial part, a core is reamed out making a clean hole into the uterine cavity at each angle. Unless the tube is very large the 7 mm. Silcock punch is the most suitable size (Fig. 1, D).

(5) Polyethylene tubing is threaded down the tube on one side across the uterine cavity from hole to hole, then down the opposite tube. The two ends of the tube can be approximated and temporarily held in a clamp.

(6) The guy sutures on the tubal flaps are then individually threaded on to a very large curved round-bodied needle which is used to transfix the sutures through the uterine wall from the cavity outwards, the flaps being directed towards the back and front. By traction on these sutures, assisted by tucking the tube down the opening with fine sinus forceps, each tube can be led into the uterine cavity using the smooth plastic tube as a guide, and then anchored by tying the sutures. As before, a few fixation sutures are inserted to anchor the peritoneum of the tube to the external margins of the openings (Fig. 1, E).

(7) About 6 inches of polyethylene tubing projecting from the fimbriated end is left to lie comfortably in the right iliac fossa. The longer end, projecting from the left tube, is brought out to the skin surface in the left iliac fossa. This is accomplished by puncturing the parietes with the trocar and cannula, withdrawing the obturator and threading the tubing down the cannula, which is then withdrawn over the tubing. The redundant tube is knotted into a coil and sutured in about 3 places to the skin, using braided nylon.

(8) Antibiotics are given and the tube removed in 10 or 12 days.

It will be seen that this operation differs from the preceding one in that no sagittal incision mutilates the uterus, clean holes are reamed from without, rather than made by forcible disruption from within, and a polyethylene internal "stint" is used to guide the tube into its new insertion and retained *in situ* to assist the anastomosis. In the first few cases using polyethylene, a separate piece was used for each tube, and the ends brought down through the cervix, but this method of withdrawal has been discarded.

It is not advisable to perform tubal patency tests after implantation operations for at least 6 months, and even then they are found to be unreliable. After implantation by the reaming technique the tubes have been found on occasions to be so freely patent that the radio-opaque material passed directly into the peritoneal cavity, sustaining almost no pressure in the uterus. The disadvantages if any, of such a deficiency in the uterine wall leading directly into the peritoneal cavity, have yet to be determined. Since the end of 1952 the reaming technique with anastomosis over the plastic "stint", has been used in 10 cases but it is too early to assess its merits. Prior to that time, 27 operations were performed using the older less refined method first described, and the cases reported in the series are entirely of this type.

Report of Cases

In the series of 27 cases which are set out in Table I the following points are worthy of note.

FIG. 2

Interior of uterus removed at 7 months of gestation for intra-abdominal haemorrhage, showing interstitial implantation of the placenta after tubal implantation for sterility.

TABLE I

Results in First 27 Operations for Tubal Implantation

Result	Remarks	Cases
No Pregnancy—19 Cases	Post-operative evidence tubal patency	7
	No post-operative evidence tubal patency	8
	Post-operative status unknown	4
Unsuccessful Pregnancy—3 Cases	One abortion	1
	One abortion, one accidental termination	1
	Interstitial implantation, rupture 7 months	1
Successful Pregnancy—5 Cases	One child	1
	One child, now pregnant 6 months	1
	Two children	2
	Three children	1

(1) The first operation was performed 7 years ago and the last approximately 18 months ago.

(2) On 3 occasions, after laparotomy and inspection, the abdomen was closed, as the tubal damage was of such a degree as to preclude operative attack. These are excluded from the series.

(3) On 2 of the cases which are included, only one tube was implanted, the other being useless. In yet another case one tube was accidentally dislodged at the conclusion of the operation and was not re-implanted.

(4) Minor pelvic damage was present in a few. This included lesser degrees of pelvic adhesions, endometriosis of rectovaginal septum in one case, and Salpingitis Isthmica Nodosa in another.

(5) The follow-up is not complete as regards tests for patency or subsequent pregnancy, cases having been followed for variable times before becoming untraced. It is unlikely however that the results are much different from those indicated.

(6) Post-operative investigation, both by gas insufflation and radio-opaque injection, was found to be unreliable and variable. When repeated or cross-checked, an undoubted positive test was sometimes obtained after several negative ones. In several cases the opaque material entered the tubes through the anastomosis but appeared to be blocked at the fimbrial ends, although the short implanted tubes seem to lose their peristalsis and be peculiarly liable to stasis without showing spill. In all, post-operative insufflation was performed 44 times, and X-ray examination 14 times.

(7) Cases recorded as showing some evidence of post-operative patency include those in which any one test was an undoubted positive, particular attention being paid to shoulder pain; or some degree of free intraperitoneal spill of lipiodol.

COMMENTS

Consideration of the Table discloses that 19 of the 27 operations produced no known pregnancy although about half of these cases showed some evidence of tubal patency. Of the 8 cases which became pregnant 3 were unsuccessful. One of these had a spontaneous and uncomplicated abortion at 3 months. The second case with 2 abortions became pregnant with positive urine test, but at 3 months she had continuous bleeding with shrinkage of the uterus and was kept under observation as a missed or incomplete abortion. The urine test became negative and she was finally curetted from the hospital waiting list some months later. Most unfortunately the first abortion must have been completed and a new fresh pregnancy of about 2 months gestation was inadvertently terminated. Although she has one patent tube, no further pregnancies have occurred.

Particular attention should be directed to the third of the unsuccessful cases who became pregnant 5 months after operation and had an interstitial implantation of the foetus. During pregnancy the uterus was irregular in shape and

inclined to be tender. At exactly 7 calendar months she was delivered spontaneously of a premature stillborn breech infant, following which the placenta was retained, and symptoms of shock developed with signs of an intra-abdominal catastrophe. At operation the placenta was situated in the interstitial part of the uterus and extended into the tube, which was grossly distended, thinned out, and had ruptured (Fig. 2). There was much free blood and many adhesions, and the condition necessitated a difficult hysterectomy by Professor Townsend. An almost identical case of herniation at about the same period of gestation is mentioned by Green-Armytage (1952) in his series, and it must be considered a definite and formidable risk to be weighed in the balance sheet. On the credit side there were 5 successful cases, producing between them 9 healthy children and one present well advanced pregnancy. The number which became pregnant more than once is perhaps remarkable. Of the 5 cases, one only was delivered by Caesarean section on her two occasions, the other 4 were delivered normally, 3 being parous and one nulliparous.

Summary

(1) Obstruction of the Fallopian tubes is the commonest cause of absolute sterility in a marriage.

(2) Localized blockage near the uterus, often following a normal confinement or abortion, is an important type encountered in a present-day sterility clinic.

(3) Implantation operations, in spite of earlier pessimism, have more frequent indications and greater promise of success than salpingostomy.

(4) Preservation of the intact outer fimbriated end with its "egg-catching" mechanism, even in a very shortened tube, is a factor of importance.

(5) The tube has an inherent propensity to restore the continuity of its lumen into the uterus after even a crude type of implantation procedure.

(6) A technique of such implantation is described, with later developments using the reaming procedure and anastomosis over an internal splint of plastic tubing, which should promise greater success.

(7) In a series of 27 cases, using the earlier less refined method, there were 3 cases with unsuccessful pregnancies, one of which was due to an interstitial pregnancy, and this must be considered a formidable complication of pregnancy following the operation.

(8) Five cases in the series have had successful pregnancies, producing between them 9 healthy children and one pregnancy at present well advanced.

(9) If the 3 cases submitted to laparotomy without implantation are included in the series, and the present pregnancy terminates successfully, one in 6 of all cases selected for operation achieved her object, and on an average each was rewarded with double measure.

Acknowledgment

Photographs by courtesy Dr. H. F. Bettinger, Director, Department of Pathology, The Royal Women's Hospital, Melbourne.

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AN ELECTROENCEPHALOGRAPHIC STUDY OF PATIENTS WITH TOXAEMIA OF PREGNANCY AND CONTROLS*

BY

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CONVULSIONS during late pregnancy, labour and the puerperium are usually regarded as eclampsia, that is, a terminal stage of pre-eclampsia. We have all had experience of cases with mild toxaemia who convulsed, just as we have had of cases with severe toxaemia who did not convulse. Why should one patient have a fit at a low level of toxaemia and another proceed through a most severe state and never have a fit? F. J. Browne (1946) points out clearly that eclamptic convulsions may occur without either oedema or albuminuria being present. It seems quite probable that the level of toxaemia itself has little aetiological relation to the convulsion. What, therefore, is the cause of the convulsion?

In the past we have been taught that it is caused by cerebral oedema. No real evidence has been brought forward that oedema of the brain occurs in the absence of oedema elsewhere. Furthermore, patients are seen occasionally with excessive oedema of the limbs, face and abdominal wall together with severe hypertension and albuminuria who never convulse. Are we to assume that brain oedema is not present in these cases and yet accuse it in others with no evident oedema?

Experimentally in dogs Rowntree (1923) was able to produce fits by injecting large quantities of water, and Blyth (1943) in non-pregnant epileptic patients was also able to produce fits by giving excessive water to drink over 48 hours until the body weight was increased and then followed by injections of pitressin in ½ c.cm. doses every 2 hours for 10 doses. He was able to produce 45 fits in 49 suspected epileptics. One may be tempted to think that pregnancy parallels these conditions in that there is water retention with increase of body weight plus an increasing amount of circulating pitressin. However, we all know, that epileptics, when they become pregnant, have a varying response—some improve, others are made worse.

Alkalosis is known to be another aggravating factor in epilepsy but during pregnancy we are aware that the pH remains remarkably constant at about 7·4. In 1950 Parviainen, Temmes and Soiva published a report on the effect of an acidifying salt, namely ammonium chloride, on the E.E.G. of toxaemic patients. Only 6 cases were studied and they claimed that in 2 cases of severe dysrhythmia there was a striking reduction in the dysrhythmia after a few days treatment with ammonium chloride. More evidence is required on this aspect.

Taubenhaus and Engle (1945) showed that a hypocalcaemia is sometimes associated with epilepsy. In pregnancy there is known to be a slight lowering of serum calcium to about 9·5 mg. per cent at term, but there is no evidence really to support this theory.

And finally maybe there is some hormonal factor involved in the causation of convulsions. Whatever the precipitating factor may be, and it seems likely that it may vary from patient to patient, there must be an underlying susceptible brain.

On this point I shall present to you my own work which lends support to this concept and I would also like to draw your attention to two other reports. Firstly that of Williams and Sweet (1944) concerning the constitutional factor in anaesthetic convulsions. They investigated 22 patients who had these anaesthetic convulsions and found that 75 per cent of them

* Presented at the Third Conference of Fellows and Members of the Royal College of Obstetricians and Gynaecologists, held in Melbourne on 26th and 27th August, 1954.

showed cerebral dysrhythmia. Secondly, Rosenbaum and Maltby (1943) studied 20 eclamptics and found a family history of convulsions in 12 and an E.E.G. dysrhythmia in 13. Their control series of 20 non-convulsing toxaemias gave a family history in 2 cases and these 2 also had dysrhythmia.

We in Adelaide cannot claim to have eliminated convulsive toxaemias as can the Crown Street Sydney School; for even whilst some patients have been in-patients in our antenatal wards under strict toxaemia therapy they have convulsed. Either Dr. Dixon Hughes's school was using a better toxaemia therapy than we were, or it was fortunate in having more stable cerebral rhythms in the Sydney population!

The Actual Study

The actual study was begun in the latter half of 1952 and continued throughout 1953. Ninety-eight patients in all were examined by electroencephalography. Those chosen were, firstly, all the convulsing patients, secondly, cases of toxaemia—mild, moderate or severe—thirdly, normal controls. The selection of the cases other than those who convulsed was left in the hands of the ward sister. These patients were transferred to the Anatomy School of the Adelaide University for the tests. Most of those patients in the first group were emergency admissions and were examined about 10–14 days post-partum. The majority of the remaining two groups was also examined post-partum, but some were taken from the hospital and examined antenatally to assess the prognostic value of the test. Several patients have been examined twice to test the consistency of the tracings.

Apparatus

The apparatus used was a 6-channel type with pen-writer and cathode-ray recording. A standard technique was adopted using silver–silver chloride pad electrodes retained against the scalp with a conventional hair-net. A darkened room was used to encourage relaxation and to get better alpha waves and it was usual to record for 10–15 minutes continuously in each case. Resting records from all areas, including temporal regions, were taken and then the effects of hyperventilation were recorded. This makes the brain more irritable and thus tends to show up abnormalities not present in the resting record. The ease with which abnormalities are evoked is an indication of the basic instability of the rhythmic process.

The Value of E.E.G. Records

Electroencephalographic diagnosis is not yet 100 per cent reliable but with experience it is becoming more so. The main field of investigation has been amongst the epileptics, but even now it is proving quite reliable in cases of brain tumours or other expanding cerebral lesions, traumatic lesions and vascular diseases.

In known epileptics the electroencephalogram is far from being consistent in showing dysrhythmias—only about 60 per cent of epileptics show interseizure dysrhythmias in a single test. The tracings in this investigation have all been examined and reported on by Dr. W. R. Adey, the then Reader in Anatomy, University of Adelaide, and all his reports were given in writing shortly after each tracing had been completed and before he had been told the history of the patient. This method was adopted to eliminate any criticism of bias in reading the tracings.

The arbitrary divisions shown in Table II into mild, moderate and severe are usually unsatisfactory but have been attempted as a rough guide only, when considering severity. Those included in the mild group had blood pressures not exceeding 150 mm. Hg systolic and 100 mm. Hg diastolic with 1/8 or less albuminuria after boiling and standing. The moderate group included those not in excess of 165 mm. Hg systolic and 105 mm. Hg diastolic and 1/2 albuminuria, whilst the severe were in excess of these latter standards.

Discussion

This series of 98 cases is too small from which to draw any definite conclusions. However the figures presented show a considerably higher percentage of dysrhythmia amongst the toxaemic group (54 per cent) as compared with the normal

TABLE I

Type of Case	Number	Dysrhythmia	Per cent
Convulsive Toxaemia (all were primiparae) ..	12	10	83
Non-convulsive Toxaemia	33	8	24
Essential Hypertension	15	4	
Epilepsy	2	1	
Diabetes	1	—	
Thyrotoxicosis	1	—	
Normal Pregnant Controls	34	5	15
	—	—	
Totals	98	28	

TABLE II

Type of Case	Number	Dysrhythmia	Per cent
Convulsive Toxaemia:			
Mild	2	2	
Moderate	1	—	
Severe	9	8	
	—	—	
	12	10	83
	—	—	
Non-Convulsive Toxaemia:			
Mild	12	5	
Moderate	8	2	
Severe	13	1	
	—	—	
	33	8	24*

pregnant cases (15 per cent). This is significant. Further it can be noted that 83 per cent of the convulsing toxaemic patients exhibited dysrhythmia as against 24 per cent in the non-convulsing group.

Because of the arbitrary divisions between the various grades of toxaemia and the small number of cases, it is probably unwise to dwell upon the tendency shown in the non-convulsing group; that the greater the severity of the toxaemia the more stable the rhythms.

These findings allow the suggestion that there is increased cerebral irritation present in all grades of toxaemia, but there is some additional factor required to produce the actual fit. This factor appears to be present more frequently in the clinically severe case yet it may be present in the clinically mild case.

Not enough cases were examined by electroencephalography in the antenatal period to assess its value as a prognostic measure regarding the development of convulsions. We must always remember firstly that about 15 per cent of the general population show dysrhythmia and secondly that of the known epileptics only about 60 per cent show any dysrhythmia on interseizure records. The findings in this survey suggest that anti-epileptic measures in therapy are indicated in all cases of toxaemia and especially in the severe cases.

SUMMARY

(1) There is a significantly higher proportion of dysrhythmia found amongst cases of toxaemia (54 per cent) than in cases of normal pregnancy (15 per cent).

(2) The convulsing toxaemic patients showed 83 per cent of dysrhythmias as against 24 per cent in the non-convulsing group.

(3) Increased cerebral irritation is found in all grades of toxaemia.

(4) Anti-epileptic measures are indicated in all grades of toxaemia, especially in the severe.

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PARTURITION FOLLOWING PELVIC REPAIR OPERATIONS —A NEW ZEALAND SURVEY*

BY

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THE problem of parturition following pelvic repair operations is a subject well worthy of study and a re-investigation of the indications for a repair operation is necessary in the light of the changes in the domestic life of the average woman today.

Before the war the married woman in the middle and higher income group could rely on reasonable domestic help for the rest of her life and could well afford to put off or even avoid necessary pelvic repair operations. The position is now entirely different. The aim of gynaecologists today is to keep women fit and well, able to sit or walk at will, to make them independent of others so far as body movement is concerned —in short, able to feed themselves, wash and bath themselves, able to move freely and enjoy their lives, until some other cause, e.g., chronic cardiac or rheumatic disease, limits their activities. The Mother of today with several children cannot afford to postpone a necessary pelvic repair operation. If she is incapacitated, the home suffers and the happiness of all its occupants is imperilled.

If it is agreed that a pelvic repair operation is necessary and cannot be delayed, the question of subsequent pregnancies must be considered and the effect of a pregnancy on a repair operation.

There is considerable evidence of the important role which the cervix plays in the maintenance of a pregnancy and as the commonest repair operation (Manchester) combines a partial amputation of the cervix we must first examine the activity of the cervix consequent on impregnation.

I will omit mentioning the ordinary anatomy and physiology of the cervix in this paper but would draw your attention to recent work on the behaviour of the cervix during pregnancy.

Danforth (1947) of New York states that the human cervix is composed predominantly of fibrous connective tissue not smooth muscle. The fundamental tissue of the uterine wall above the cervix is composed of smooth muscle which does not differ significantly from the smooth muscle of the corpus. By Danforth's research, therefore, it is shown that, from both functional and anatomic standpoints, the uterus must be considered as composed of two major parts: (1) cervix and (2) corpus.

During pregnancy, the classical concept is that, during the third month of pregnancy, the isthmus elongates to approximately three times its former length—this is accompanied by thinning out and subsequently unfolding occurs so that gradually the entire isthmic canal is incorporated in the ovum chamber. The isthmus is now referred to as the lower uterine segment. Unfolding stops within a few millimetres of the internal os.

In Danforth's investigation 12 pregnant and 46 non-pregnant uteri were used—considerable attention being paid to the staining and fixation of specimens so that the difference between muscular and fibrous tissue was clearly marked.

The results showed that:

(1) The basic structure of the cervix was found to be fibrous connective tissue.

In some specimens smooth muscle was found, its distribution showing great variability, its attenuated appearance making it unlikely that sphincteric possibilities could be attributed to it.

Stains for elastic tissue showed only minute amounts of these fibres.

* Presented at the Third Australian Conference of Fellows and Members of the Royal College of Obstetricians and Gynaecologists, held in Melbourne on 26th and 27th August, 1954.

As one ascends the cervix a level is reached where fibrous connective tissue gives way to smooth muscle, either abruptly or over an area of 5–10 mm.

(2) During early pregnancy the length of the cervix does not alter much.

(3) The elongation which occurs in the isthmic portion is proportional to that which occurs elsewhere in the muscularis of the corpus.

(4) Unfolding or dilatation of the isthmus occurs down to the region of the fibro-muscular junction.

During pregnancy it has been observed that the isthmic segment elongates during the third month prior to the time when the products of conception have fully utilized the space available in the corpus. This is proportional to the thickening which occurs elsewhere in the corpus, but the unfolding of that segment only occurs when the cavum corporis requires more space to expand. The unfolding accompanied by thinning stops abruptly at the fibro-muscular junction of the isthmic segment with the cervix and after unfolding it is not possible to demonstrate the junction of corpus with isthmic segment by any means—macroscopic or microscopic.

The isthmus, therefore, must be considered as part of the corpus and no reliance can be placed on it to assist in retaining a pregnancy *in utero* if the cervix is incompetent. The amount of cervix retained, therefore, in a Manchester repair operation or other cervical operations is of vital importance in any pregnancy subsequent to a pelvic repair operation (see Figs. 1 and 2).

Risk of Abortion Following Operation

There is no lack of corroboration of the incidence of abortion following pelvic repair operations in the literature. Bryan Williams (1942) quotes the after-results of 37 patients who had vaginal repair with amputation of the cervix. These 37 patients had 49 pregnancies. Of these 49 pregnancies: 4 terminated in therapeutic abortion, one having shown signs of threatened abortion, 20 terminated in abortion, 8 terminated in premature labours and only 13 terminated in full-time pregnancies.

This means that, out of 41 pregnancies,

New Zealand Survey

Contributors	No. of Cases	No. of Pregnancies	Mis-carriages	Premature Labours	Caesarean Section	Vaginal Delivery Alone	Vaginal Delivery With Episiotomy
Rutherford	4	5	1	0	2	2	0
Harbutt	16	16	0	0	9	7	0
Wright	5	5	0	0	1	0	3
Fitzgerald	5	5	1	0	0	0	4
B. M. Corkill	3	3	0	0	0	0	3
Stewart	3	5	2	1	0	1	1
Jennings	10	16	5	4	2	0	5
Giesen	6	7	1	0	0	1	5
Foate	28	30	1	1	2	0	22*
Cumming	6	6	0	0	2	1	3
Dunn	6	6	0	1	4	1	1
Doris Gordon	1	1	0	0	1	0	0
Fisher	18	8	0	0	3	0	5
T. F. Corkill	8	8	0	0	1	0	7
Averill	22	25	2	8	5	1	17
Averill (St. Helens Hospital)	5	5	0	1	1	2	2
Cox	1	1	1	0	0	0	0
Ross Gordon	2	2	0	0	2	0	0
Bruce	2	2	0	0	2	0	0

* Cases reported from Oxford Hospitals, England.

FIG. 1
Changes in the uterus during early pregnancy (after Danforth).

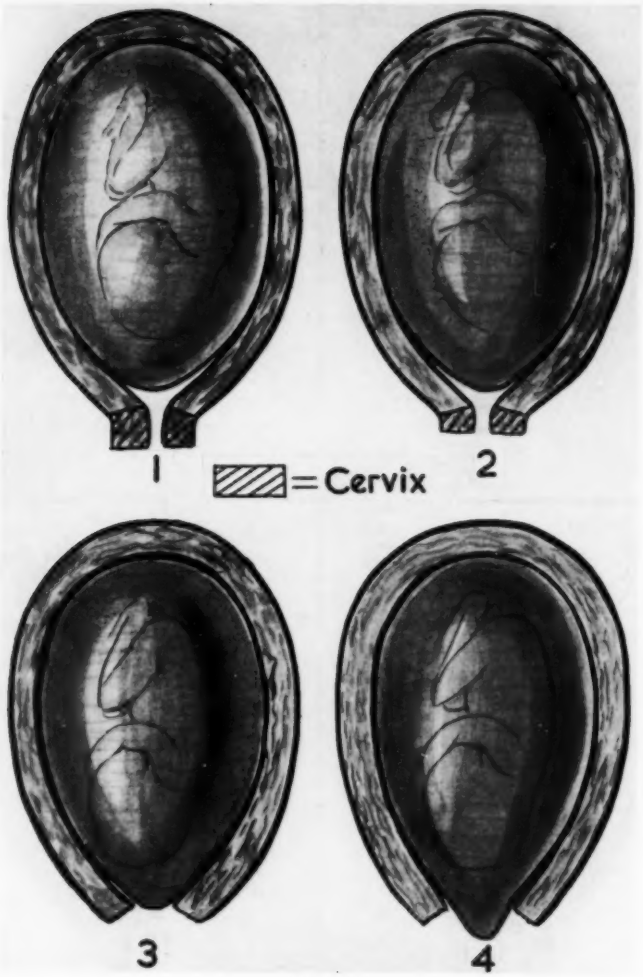

FIG. 2

The action of the amputated cervix following impregnation at 16 weeks (4 degrees).

Parturition Subsequent to the Manchester Operation
(Previously reported)

Reference	No. of Cases Manchester Operation	No. in Childbearing Period	No. of Deliveries	Subsequent Recurrence	Operative Delivery
Maier and Thudium	138	47	13	0	Inst. 3
Fletcher Shaw	664	—	30	5	0
Gordon	358	58	18	1	Inst. 8 C.S. 1
Hunter	19	19	1	0	0
*Fothergill	156	—	32	1	Inst. 23
Leventhal and Boshes	51	—	1	0	0
Salmon	254	—	2	0	0
Herzfeld and Tod	132	—	11	0	Inst. 3
Williams	45	45	27	0	0
Bazan and Althabe	354	—	8	0	Inst. 1
Borras	145	—	4	0	0
Lacey	521	382	89	33	Inst. 35

* Included in Lacey's figures.

excluding the therapeutic abortions and cases not delivered at time of writing, abortion or premature labour had occurred 28 times or in 68 per cent.

Among my New Zealand contributors 12 out of 22 considered the risk of abortion a feature following these operations and should be guarded against, if possible, at the time of operation; only one out of the 22 did not consider the risk of abortion increased above the normal rate.

Additional support also comes from Montgomery (1950) writing in Meigs and Sturgis's book *Progress in Gynecology* where he states "If the patient is in the child-bearing period of life and is likely to have further pregnancies, the cervical amputation should be limited".

There is, therefore, considerable evidence to prove that abortion following operation is a definite possibility and must be taken into account in the planning of such an operation during the child-bearing period of life.

Dystocia Following Operation

There are numerous reports in the literature as to the possibility of dystocia in pregnancies subsequent to a pelvic repair operation and caution is recommended.

(*a*) Hunter (1939) reports 5 cases of Caesarean section performed at or near term for stenosis of the cervix.

(*b*) Murray L. Brandt (1933) of New York reports Rawl's survey of cases of labour following cervical operations in which it was found that there was re-laceration in 40 per cent of patients with a cervical amputation. He mentioned 3 cases of Caesarean section where the cervix showed no prospect of safe dilatation.

(*c*) Leonard (quoted by Brandt) at Johns Hopkins Hospital reported difficulty in 7 out of 11 cases of first birth following cervical repair.

The danger from cervical dystocia appears to come from cicatricial contraction of the cervix, possibly following sepsis, causing a firm rigid cervix which will not dilate and allow descent of the foetus.

In such cases the presenting part will remain high until the onset of labour; the incidence of premature labour is not a feature; and the pregnancy is liable to be carried beyond term. In these cases, which are almost certainly in the last decade of child-bearing life, the treatment clearly indicated is Caesarean section.

My New Zealand contributors did not consider cervical dystocia a problem but, as the majority of them (14 out of 22) favoured Caesarean section, the syndrome was probably not allowed to show itself.

Perineal Arrest

Having passed the cervix the foetal head will enter the vagina and come in contact with the

pelvic floor. In my cases the anterior vaginal wall does not generally suffer trauma provided an adequate episiotomy is performed. In any accurately healed perineal repair the approximation of the rectal fascia supported by a drawing together of the levatores ani muscles assures a satisfactory perineal support. The repair of the laxity or stretching in the rectal fascia ensures a good functional result. Prolonged pressure from the foetal head on the pelvic floor will stretch the fascial supports even although no mucosal tear occurs and the good functional result of the pelvic floor repair operation will be undone.

A satisfactory episiotomy operation with delivery of the child by forceps if necessary and an accurate repair of the episiotomy is the answer here. In the 25 cases which I present in this paper, delivery by forceps with episiotomy was effected in 17, whilst 1 only delivered herself vaginally without episiotomy; 5 cases out of the 25 required Caesarean section; 8 of the cases had a premature labour and there were 2 miscarriages. One patient has had 3 vaginal deliveries following her repair operation in this series and she now shows signs of needing a further posterior repair operation sometime in the future but her anterior vaginal wall has not suffered to any extent. The cystocele with stress incontinence was the main indication for the repair operation originally.

In the table below, of the combined experience of my New Zealand colleagues including my own, it will be seen that out of 156 pregnancies reported following pelvic repair operations vaginal delivery alone was reported in 16 cases

Results of Pregnancies

		Percentage to Total Pregnancies
No. of Contributors (all F.R.C.O.G. or M.R.C.O.G.)	18	
Total No. of Pregnancies	156	
Miscarriages	14	8·9
Premature Labours	16	10·2
Caesarean Section	37	23·6
Vaginal Delivery (alone)	16	10·2
Vaginal Delivery (with episiotomy)	78	50·0

or 10·2 per cent and vaginal delivery with episiotomy in 78 cases or exactly 50 per cent. Added together this makes an overall total of deliveries per vaginam of 94 cases or 60 per cent.

Choice of Operation

Firstly we must decide what is the optimum time for repair operations? In my opinion the answer is a simple one: "When they are necessary."

Having decided that an operation is necessary and cannot be delayed, the next important decision is to decide on the type of operation. This is subject to variation in the experience of the operators.

The operation with the most universal application is the Manchester operation and this operation is satisfactory in most cases. The length and descent of the cervix must, however, be carefully considered. There is considerable variation in the human species in the length of the cervix. I have seen some women with such a short cervix that they are unable to retain a pregnancy after the 3rd to 4th month; others have only been able to carry a pregnancy to term by resting most of their pregnancy in bed, and thus taking as much pressure as possible away from the incompetent cervix. In other cases the cervix is so long that reasonable amputation does no harm. It is important, however, in performing this operation to remember the fibrous nature of the cervix and the unfolding of the isthmus which takes place during the earlier months of pregnancy.

The repair of the anterior vaginal wall and the perineum proceed on the usual lines, but I would stress the necessity for adequate fascial and muscular support rather than a reduction of the skin area only with approximation of its edges.

The question of whether or not to combine the repair with an abdominal operation to plicate the round ligaments with silk or perform some similar suspensory operation is a matter which requires careful thought. The tall asthenic young woman with the large, retroverted, mobile uterus and probably a prolapsed ovary will be rendered much more comfortable and less likely to have a recurrence of her prolapse if some simple intra-

abdominal support is given in addition to her Manchester repair. Te Linde and E. H. Richardson (1943) state: "It is our opinion that these patients who expect to have further children are best treated by the combined procedure of a suitable plastic vaginal repair coupled with some type of intra-abdominal suspension." The abdominal portion is very simple and it prolongs the operation by barely 10 minutes.

In the experience of myself and my colleagues, however, there is a considerable preference for the Manchester operation. Out of 22 contributors, 20 prefer the Manchester operation, either to the exclusion of all others or in an overwhelming proportion, and only 5 consider that additional abdominal support is sometimes advisable. These figures give, I think, a reasonably accurate summary of the position among gynaecologists generally.

Management of Pregnancy Following Operation

There is now the important task of guiding the patient through her subsequent pregnancy. The dangers are these:

(1) Greater tendency to abort.
(2) Greater tendency to premature labour.
(3) Necessity for accurate antenatal care and careful assessment at the 36th week as to contracted pelvis, disproportion between maternal pelvis and foetal head, and engagement of foetal head in pelvis.

(1) With regard to the greater tendency to abort—adequate rest with sedation is generally all that is necessary. During the first 4 months there is a greater risk, particularly at the time of the suppressed menstrual period. At that time bed rest is advisable. The question of any further treatment, e.g., hormones, is beyond the scope of this paper.

(2) Premature labour is a distinct possibility from the 6th month onwards and is due to the shortened cervix being gradually drawn up and not leaving sufficient to retain the foetus *in utero*. Labour is initiated. It is on this account that it is necessary to leave *in situ* some of the fibrous cervix to keep it effective. Sometimes scar tissue forms at the site of amputation, which acts in the same way as the fibrous tissue of the cervix, but it is not inclined to dilate during labour so satisfactorily.

(3) Antenatal care. The necessity for adequate antenatal care can hardly be over-emphasized. Having survived the risk of miscarriage, it is necessary for the obstetrician to observe the behaviour of the cervix as the pregnancy advances. A dilating incompetent cervix is an indication for increased bed rest. This precaution may allow the pregnancy to advance from the stage where the infant is too premature to survive to where it is possible, with care, to save a premature baby.

At the 36th week examination, it is necessary to decide on the method of delivery. The chief points to be noted here are:

(1) Head fitting into pelvis with no apparent disproportion and no narrowing of the maternal pelvis. Here the patient may proceed to a trial of labour.

(2) A vaginal examination will ascertain the condition of the cervix and the pelvic floor. If the pelvis is contracted and the child's head not entering the pelvis, elective Caesarean section may be decided on. From the vaginal examination, the possibility and advantage of inducing premature labour will be easily discernible.

(3) The nervous disposition of the patient and her attitude to the labour requires study. In some patients there is a very genuine fear that a vaginal delivery may render a further repair operation necessary. This fear is not entirely unfounded; Fletcher Shaw (1933) reports the results of 27 pregnancies following Manchester repair operation, in which 5 had some signs of recurrence. In these cases, where the patient is unduly fearful of a recurrence, the decision might be made in favour of a Caesarean rather than a vaginal delivery particularly if sterilization is considered advisable.

Management of Labour

The first essential is that the patient must be confined in a fully equipped obstetric hospital capable of handling every form of obstetrical operation.

In the case where a trial of labour has been decided on, the average patient will dilate the cervix without difficulty and the foetal head

enters the pelvis. When this stage is reached, the patient is anaesthetized in the lithotomy position. A deep episiotomy is performed, the child delivered with forceps and the episiotomy repaired. This sequence should not weaken the repair operation and is advisable even if the labour is premature.

On the other hand, if the cervix is cicatrized and will not dilate fully, an obstructed labour can develop with possible rupture of the uterus. Caesarean section is necessary in such cases.

It is interesting to note that in 1921 Fothergill reported that out of 156 Manchester operations: 30 children were born to 24 patients of which 23 were natural deliveries; 7 were instrumental and in no case was labour obstructed and 4 patients had 2 labours each with no recurrence and 1 patient had 1 labour and was badly torn with recurrence of rectocele—not requiring treatment. Another had 1 labour and says "the womb falls slightly if tired" but does not require further treatment. One patient had had 3 labours following operation and now requires a further operation.

A small proportion (3 out of 22) of my contributors favour surgical induction of labour at 38 weeks. This in many cases is good treatment but the sequence of events in these cases renders any hard and fast rule inadvisable. If the patient has reached term with the presenting part still above the pelvis and the child of at least normal proportions, then a Caesarean section is prudent treatment.

Conclusions

(1) Pelvic repair operations are now necessary, in many cases, owing to our changed domestic life, in an earlier age group than was considered necessary previously.

(2) These operations can be undertaken with a view to further pregnancies without serious risk of recurrence.

(3) Some slight alteration in technique is necessary in that cervical amputation should be limited.

(4) To ensure a live baby and an undamaged mother, a higher proportion of pregnancies should be delivered by Caesarean section than is necessary in ordinary deliveries.

(5) If not delivered by Caesarean section all cases should be delivered by episiotomy, instrumental delivery and repair unless the foetus is very small.

(6) All births in patients subsequent to a pelvic repair operation must take place in a fully equipped obstetric hospital.

Summary

(1) A review of our ideas on pelvic repair operations in relation to subsequent childbirth is presented.

(2) Opinions from 22 contributors are quoted and figures in relation to their cases treated are supplied by 18.

(3) All the contributors are practising in New Zealand and all hold the qualification of F.R.C.O.G. or M.R.C.O.G.

(4) The operation of choice is the Manchester operation. Twenty out of 22 contributors favour this operation.

(5) The number of cases presented by the contributors is 156. The results of these pregnancies showed that Caesarean section was considered necessary in 37 cases or 23·6 per cent, vaginal delivery was conducted in 94 cases or 60·2 per cent in which episiotomy was performed in 78 or 50 per cent of cases, and vaginal delivery alone in 16 cases or 10·2 per cent.

(6) The recent work on the functions of the cervix consequent on impregnation is presented in its relation to operations on the cervix.

(7) Comparative figures previously published in the literature are quoted.

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A CASE OF CERVICAL PREGNANCY

BY

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IMPLANTATION of the fertilized ovum in the mucosa of the cervical canal results in one of the rarest forms of ectopic gestation. Pregnancy usually terminates by abortion within the first 2 or 3 months and, the cervical canal being a relatively inefficient nidation site, it may be that other cases terminate within the first few weeks and so escape detection and recognition. The majority of the cases reported have presented with painless vaginal bleeding.

The most comprehensive reviews on the subject are those by Studdiford (1945) and Schneider (1946), the latter accepting as definitely proven only 12 cases in the world literature.

The establishment of a diagnosis of cervical pregnancy demands, when possible, thorough anatomic-histological examination to exclude a pregnancy in the isthmus of the uterus or an ordinary abortion from the uterus. The diagnosis in many of the cases so far reported has been based on clinical evidence alone or on inconclusive pathological data.

A case report of a 4–6 weeks old cervical pregnancy, confirmed by biopsy examination, follows.

CASE RECORD

A woman, aged 35, para-1, gravida-3, was admitted to St. Luke's Hospital, Bradford, on 19th November, 1953, complaining of painless vaginal bleeding. Bleeding began on 17th November but the next day became more profuse, with the passage of clots. Her menstrual periods had occurred regularly every 28 days and lasted for 4–6 days: her last period was about 6 weeks before the onset of bleeding.

On admission she was slightly shocked (temperature 99·2 °F., pulse 92, blood pressure 110/65 mm. Hg, haemoglobin 6·4 g. per cent). On vaginal examination the external os was found to be dilated, admitting the tip of one finger, with a blood clot protruding. An incomplete abortion was diagnosed. After this examination her blood pressure fell to 90/60 mm. Hg and treatment for shock was instituted.

Subsequent examination under anaesthesia on 19th November revealed a red, friable "tumour", about 1 cm. in diameter, attached to the posterior lip of the external os at about the "4 o'clock" position. After removal of the "tumour" by sponge-forceps the raw area of the cervix bled freely. The uterus was of normal size, anteverted and not softened; the uterine adnexa appeared to be normal.

Dilatation and curettage of the uterus were performed and profuse, friable curettings were obtained. A biopsy was taken from the raw area of the cervix as malignancy could not be excluded with certainty.

The patient made a good clinical recovery following a course of intravenous iron therapy and she was discharged on 2nd December, 1953.

Previous medical history

The patient had a normal full-time pregnancy in 1938. In 1945 she aborted after about 3-months gestation and was treated by uterine curettage. In 1951 she was admitted to St. Luke's Hospital, Bradford, complaining of dyspareunia and lower abdominal pain. Examination at this time revealed a prolapse of the uterus, almost of second degree, with an erosion of the cervix. The cervical canal was indurated, thicked and stenosed; dilatation was effected with some difficulty and uterine curettage was performed. The endocervical canal was then cauterized by silver nitrate.

In 1952 she was readmitted to St. Luke's Hospital again complaining of dyspareunia, pain in the left iliac fossa and backache. Anterior and posterior colporrhaphy, and uterine curettage, were performed; the cervix was not amputated.

She again aborted in May, 1953, after about 3-months gestation, and was treated by uterine curettage. Six months later her present trouble began.

HISTOLOGY

The "tumour" removed from the cervix (Fig. 1, C) is composed of a thin strip of cervical tissue (Fig. 1, c) overlying blood clot in which is

embedded chorionic tissue; chorionic elements can be seen adjacent to decidual cells just beneath the endocervical surface (Fig. 5). A few distorted endocervical glands are present but the surface epithelium is absent.

The biopsy specimen of cervix has broken into two portions (Fig. 1, A and B). One portion (Fig. 1, A) contains chorionic tissue embedded in blood clot beneath a thin layer of cervical tissue which shows decidual change (Figs. 2 and 3). The epithelium covering the endocervical surface is absent but at one point (Figs. 2 and 4) squamous epithelium overlying endocervical glands is seen. The other portion (Fig. 1, B) is composed of cervical tissue which shows increased stromal fibrosis but no evidence of decidual change; this portion is covered in part by squamous epithelium. Squamous metaplasia of the epithelium in one endocervical gland is seen and one gland-acinus shows cystic dilatation (Fig. 1, b).

The uterine curettings (19th November, 1953) are endometrial fragments showing a well developed decidual reaction; no chorionic tissue was found in the uterine curettings.

The histological appearances indicate that the ovum was implanted in the cervix at about the junction of the endocervical with the squamous epithelium. Following the invasive trophoblastic activity interstitial haemorrhage has resulted in disruption of the cervical tissues with "tumour" formation at the site of implantation. The histological appearances of the chorionic tissue are consistent with an estimated 4–6 weeks gestation period.

Discussion

This case confirms the generally accepted view that implantation of the fertilized ovum in the endocervical mucosa can occur. The possibility of secondary implantation in the cervical canal cannot be excluded entirely, however, although the histological evidence does not suggest this.

Nothing definite is known of the aetiological factors which determine cervical implantation. Studdiford (1945) considers it possible for the fertilized ovum, under influences "unknown but probably largely accidental", to traverse the uterine cavity during its period of maturation development (7–10 days) and implant in the cervix, or, as Suzuki (1949) puts it, the ovum is acted on by "unknown factors which either delayed maturation or hurried it through the uterine cavity".

Delayed fertilization has been suggested as a possible aetiological factor by Ellingson (1950).

It is of course not known how often a fertilized ovum escapes from the uterus but the possibility exists and if we postulate that a cervical pregnancy may result when such an escaping ovum is entrapped in the endocervical canal then it would appear reasonable to expect this occurrence to be more likely in an abnormal cervix. In the present case fibrous stricture of the cervical canal had been diagnosed 2 years previously. Cervical lesions, such as chronic infection or lesions resulting from trauma at the time of previous deliveries or abortions, are also more likely to be encountered in the older age groups.

This conjecture is supported in some measure by an analysis of the ages and obstetrical histories of cases which have been reported, in good faith, as examples of cervical pregnancy (Table).

Of 56 cases, in which the age is stated, 88 per cent of the patients were 25 years of age or more, 63 per cent were 30 years of age or more, and 48 per cent were 35 years of age or more. Of 53 cases, in which obstetrical histories are provided, 76 per cent of the patients had already been pregnant, while at least 81 per cent had either already been pregnant or had undergone some gynaecological operation or had shown some cervical abnormality.

The accuracy of the diagnosis in many of the above cases is, however, undoubtedly open to question. Many more histologically proven cases must be studied before we can accept as the determining aetiological factor either an ovum being acted on by "unknown" or "accidental" factors of the earlier writers, or the suggestion now offered that an escaping fertilized ovum is entrapped in a previously diseased cervix.

Summary

The case is described of a 4–6 weeks old cervical pregnancy, confirmed by histological examination, and it is the first proven case we have been able to find in the British literature.

TABLE

*Cases Reported, since 1900, as Examples of Cervical Pregnancy**

Author	Age	Obstetrical History†	Author	Age	Obstetrical History†
Kermauner (1906)	37	P.8.	Desirotte (1940)	38	P.0. G.1.
Jaschke (1910)	39	P.7.	Reist (1941)	34	P.3. G.6.
Pankow (1910)	46	P.9.	Bowles (1945)	28	P.0. G.2.
Devraigne (1911)	39	P.2. G.6.	Fearl (1945)	40	Several induced abortions.
Rubin (1911)	28	P.2. G.5.			
Tiegel (1915)	36	P.3. G.6.	Studdiford (1945)	40	P.1. G.2.
Reinhardt (1924)[1]	24	P.0. G.1.	Studdiford (1945)	22	P.0. G.1.
Wolters (1924)	26	P.3. G.5.	Schneider (1946)	40	P.1. G.2.
Bacialli (1926)	36	?	Dougal (1947)	39	P.2. G.3.
Iolkin (1926)	35	P.0. G.3.	Fuster Chiner and Queralt Ballester (1948)	36	?
Schneider (1926)	27	P.0. G.2.	Morton (1949)	26	P.1. G.2.
Bacialli (1927)	25	P.1. G.2.	Morton (1949)	28	P.0. G.2.
Bacialli (1927)	32	P.0. G.1.	Schultheiss (1949)	39	P.1. G.2.
Gänsbauer (1927)	32	P.1. G.2.	Suzuki (1949)	37	P.5. G.6.
Strezow (1927)	24	?	Suzuki (1949)	41	P.1. G.7.
Steinbiss (1928)	30	P.0. G.2.	Dubuis (1950)	28	P.5. G.7.
Kleiner (1929)	23	P.1. G.3.	Ellingson (1950)[2]	38	P.0. G.1.
Meyer (1929)	27	P.0. G.1.	Ellingson (1950)	21	P.0. G.1.
Tropea (1929)	29	P.2. G.4.	Ellingson (1950)	25	P.1. G.3.
Tropea (1929)	38	P.6. G.15.	Oswald (1950)	35	P.1. G.3.
Bolaffi (1933)	37	P.1. G.2.	Duckman (1951)	34	P.0. G.1.
Bolaffi (1933)	39	P.1. G.2.	Fleischhauer (1951)	37	P.0. G.1.
Crousse (1934)	37	P.7. G.8.	Vogt *et al.* (1952)	37	P.2. G.4.
Otto (1934)	30	P.1. G.4.	Baptisti (1953)	17	P.0. G.1.
Gergely (1935)	37	P.0. G.1.	Baptisti (1953)	21	P.1. G.2.
Hyslop (1935)	35	P.0. G.1.	Lucci (1953)	26	P.2. G.3.
D'Aprile (1937)	32	P.1. G.2.	Marsh and Schuyler (1953)[3]	25	P.0. G.1.
Schürger (1937)	32	P.2. G.3.	Present Case	35	P.1. G.3.
Wittrin (1938)	29	P.2. G.4.			

[1] Curettage of uterus 6 months previously.
[2] Dilatation and curettage of uterus 6 years previously and "examination for sterility" 1 year previously.
[3] Curettage and cauterization of cervix for erosion 2 years previously.

* This list is not fully comprehensive as several references in continental European literature have not been available for consultation.
† P=Para. G=Gravida.

A brief review is made of previously reported cases.

Factors which may determine implantation of the fertilized ovum in the endocervical mucosa are discussed, and the suggestion is offered that structural abnormality of the cervix is a predisposing factor.

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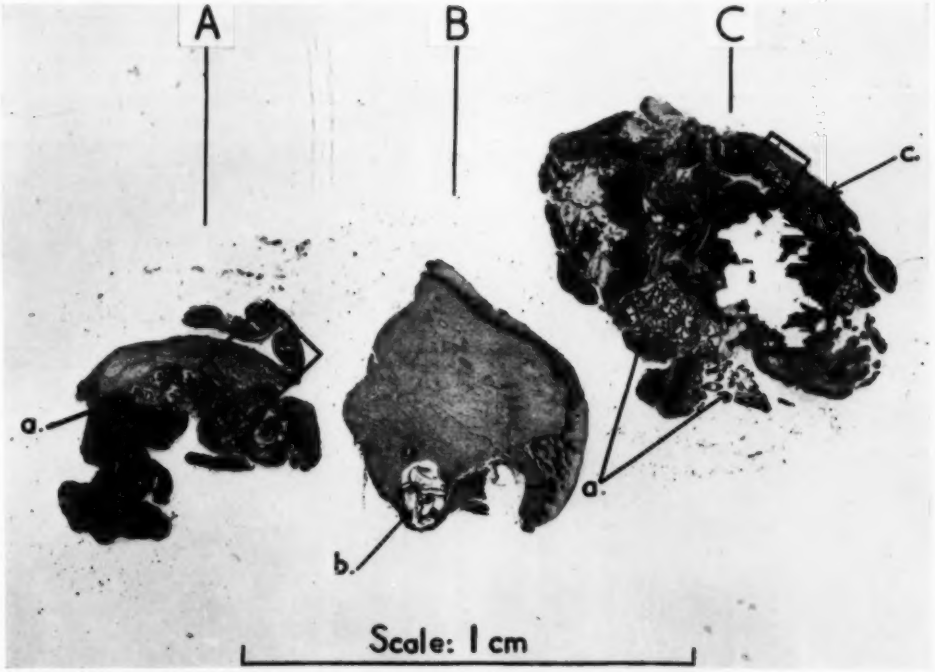

FIG. 1

Fragmented cervical biopsy specimen (A and B) and the "tumour" (C) which was removed from the lip of the external os and is composed of a thin strip of cervical tissue (c) overlying blood clot. Chorionic villi (a) and a cystic endocervical gland (b) are visible. H. & E. ×7.

FIG. 2

Blood clot containing chorionic elements beneath a thin layer of cervical tissue which is covered in part by squamous epithelium; endocervical glands can be seen. The cervical tissue has been disrupted by interstitial haemorrhage. (This section was cut from the same block as in Fig. 1, A (in square) but cut at a slightly different level.) H. & E. ×22.

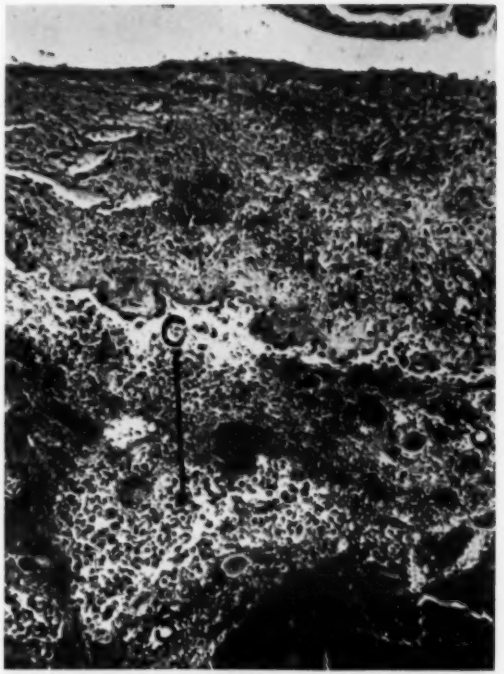

FIG. 3

A thin strip of cervical tissue, showing decidual change, overlying blood clot in which syncytio- and cyto-trophoblastic cells (S and C) can be seen. (Fig. 2, in larger square.) H. & E. ×45.

FIG. 4

Squamous epithelium overlying endocervical glands: decidual change of the stromal cells is present. (Fig. 2, in smaller square.) H. & E. ×75.

FIG. 5

Chorionic elements adjacent to decidual cells beneath the endocervical surface; the covering epithelium has been eroded. (This section was cut from the same block as in Fig. 1, C (in square) but cut at a slightly different level.) H. & E. ×70.

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INCISION OF THE CERVIX

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"Know one false step is ne'er retrieved,
And be with caution bold."

T. Gray.

INCISION of the cervix remains a controversial subject upon which opinion is deeply divided. Its opponents, whilst admitting its possibilities, condemn it as a dangerous procedure, and point to the relative safety of the lower segment Caesarean section.

Its proponents, in order to justify the operation, must examine its hazards both immediate and remote, and devise a method of selection and an operative technique which will avoid them and, in the cases so selected, render the operation easier, quicker and safer than any other.

The object of this communication is to show (as the result of observations made on the cervices of 155 primigravidae) that the operation has a real but strictly limited use.

INSPECTION OF THE CERVIX OF 155 CONSECUTIVE PRIMIGRAVIDAE IMMEDIATELY FOLLOWING DELIVERY, AND AGAIN AFTER 6 WEEKS

This investigation was carried out to determine the site, size, and incidence of cervical tears in spontaneous delivery and forceps delivery at full dilatation, and to obtain some guide as to the optimum site for cervicotomy, and the necessity for repair. It was also felt that, if cervical tears were the rule in spontaneous delivery, then cervicotomy need not be regarded as an heretical procedure.

Of the 155 patients whose cervices were inspected immediately after delivery, 125 (81 per cent) had delivered spontaneously, and 30 (19 per cent) had been delivered with forceps. Of the latter, 3 had had cervicotomy, and in the rest the cervix had been at full dilatation.

Of the cervices inspected, 90 (58 per cent) were lacerated. Of the 125 following spontaneous deliveries, 74 (59 per cent) were lacerated, and of the 30 following forceps deliveries 16 (53 per cent) were lacerated or incised. Of the 90 cases in which cervical lacerations were found, 62 (69 per cent) had a single laceration, and 28 (31 per cent) had bilateral lacerations. In no case were more than 2 lacerations found. In Table I it will be seen the larger the lacerations, the greater the likelihood for them to be bilateral.

The location of the cervical lacerations is of particular interest. In 71 cases, i.e., 79 per cent of those in which lacerations occurred, the tears were at 3 o'clock or 9 o'clock, or both. In the remaining 19 cases (21 per cent), the tears occurred at 6 o'clock, and all but 2 of these were single. Of the 71 lateral lacerations, 25 occurred at 3 o'clock only, 18 at 9 o'clock only, and 28 were bilateral. *No tears were found in the anterior half of the cervix.*

There were 9 cases of severe oedema of the anterior lip of the cervix, of which only 4 had bilateral lacerations of more than 4 cm.

A summary of these figures is given in Table II, in which it is shown that there is no significant difference in the percentage incidence of cervical lacerations (excluding incisions of the cervix) between the series following spontaneous and that following forceps deliveries.

Of the 155 patients where cervices were inspected, 140 (90 per cent) returned on the 6th week to the Post-Natal Clinic. These were examined with regard to scars, ectropion and erosion, and the findings are summarized in

TABLE I

Size of largest cervical laceration	Ninety cases of lacerated Cervix grouped according to number and size of tears		Percentage with 2 tears
	One Tear	Two Tears	
Small 1½ cm.	37	10	21
Medium 1½ to 3½ cm.	21	11	34
Large 3½ cm.	4	7	64

TABLE II

Size of largest cervical laceration irrespective of number of lacerations	Following all deliveries		Following spontaneous deliveries		Following forceps deliveries	
	No.	Percentage of total deliveries	No.	Percentage of spontaneous deliveries	No.	Percentage of forceps deliveries
Cervix intact	65	42	51	41	14	47
Cervix lacerated	90	58	74	59	16	53
Small tears 1 cm.	47	31	41	33	6	20
Medium 1 to 3½ cm.	32	20	28	22	4	13
Large 3½ cm.	11	7	5	4	*6 (3)	20 (10)
Total Cases	155	100	125	100	30	100

* Three of these were incisions of the cervix and the corrected figures are shown in brackets.

Table III. As shown by the figures in brackets, the percentage incidence of cervical disease increases according to the length of the original laceration. No doubt this would have been more marked, had not 5 of the large lacerations been repaired at the time of delivery.

THIRTEEN CASES OF INCISION OF THE CERVIX

All these were primigravidae of 38 or more weeks pregnant. There was no maternal mortality, and, apart from one patient who developed bronchitis on the twelfth day, no maternal morbidity. The 16 babies were delivered without any perinatal mortality or morbidity.

The cervix was incised at 9 o'clock and 3 o'clock in all but 2 cases, and in these a single incision was made at 9 o'clock. Immediate repair was performed in all cases, and they all healed perfectly. There were no cases of ectropion, there was a small erosion in one case which healed following cauterization and, though a tiny notch was evident in 6 cases, it was not sufficient to give the impression of two definite lips.

THE HAZARDS OF CERVICOTOMY

It is necessary to analyze these before describing the operative technique, and proceeding to a consideration of the indications. They are as follows: (1) extension of the incisions, (2) obstetric shock, (3) infection, (4) residual cervical disease, (5) subsequent obstetric difficulty and (6) increased foetal mortality and morbidity.

1. *Extension of the cervical incisions.* The degree of dilatation of the cervix is not important. The determining factor is whether or not the greatest diameter of the head has descended below the cervico-vaginal junction, and here a consideration of the mechanics of the operation is most important.

In Figures 1 and 2, A A represents the direc-

TABLE III
(Percentages in brackets)

Size of largest laceration	Cases seen at P.N.C.	Residual cervical disease as seen at P.N.C.			
		Unilateral scars	Bilateral scars	Ectropion	Erosion
Cervix intact	60	1	2	1	9
Cervix lacerated	80	11	11	6	9
Small tears	40 (100)	5 (12)	4 (10)	2 (5)	5 (12)
Medium tears	31 (100)	3 (9·7)	4 (13)	2 (6·4)	2 (6·4)
Large tears (repaired 5)	9 (100)	3 (33)	3 (33)	*2 (22)	2 (22)
Oedema of Anterior Lip	9	1	8	6	2

* Neither of these cervices had been repaired at the time of the original inspection following delivery.

tion of the force when traction is applied to the forceps. This force is the resultant of A B and A C, the first being tangential to the point of contact between the head and the lower segment of the uterus, and the second at right angles to it.

In Figure 1 it can be seen that there is no resultant force in the direction of the broad ligament and uterine vessels and, in this type of case, the cervix can be safely incised to the level of the greatest diameter of the foetal head, and traction applied in the knowledge that upward extension cannot take place. Here I should like to stress the importance of particular gentleness in applying forceps in those cases in which the cervix has been incised before application is made, as one is then introducing a potential force in an upward direction. Furthermore, the head must not be displaced upwards when performing manual rotation, as the natural elasticity of the lower uterine pole will cause it to contract below the greatest diameter of the head and create the conditions indicated in Figure 2.

If the forceps are applied before the head has passed the cervico-vaginal junction, not only may the incision include the main uterine vessels, but the resultant force A C would cause tearing of the base of the broad ligament (Fig. 2).

2. *Obstetric shock*. In none of the 13 cases

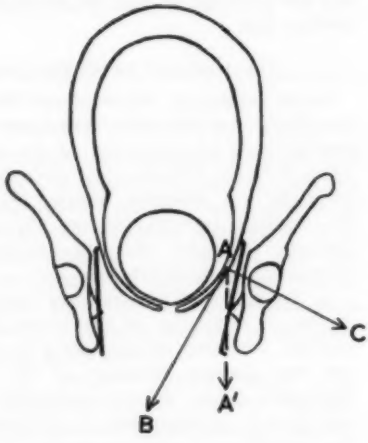

FIG. 1

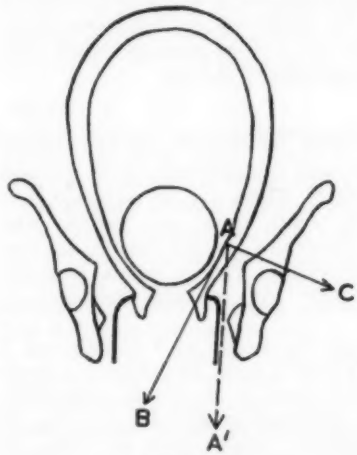

FIG. 2

was there any clinically observable obstetric shock. In 9 labour was prolonged for more than 48 hours, and the average length of labour for these was 96 hours. Sheehan (1948) points out that prolonged labour is an important predisposing factor in obstetric shock, and yet, despite this, shock did not follow the operation in any of this series.

3. *Infection.* The tissue planes opened up are not as extensive as in Caesarean section, and the absence of morbidity in this series does not point to infection as a serious hazard.

4. *Resultant cervical disease.* With proper siting and repair of the incisions this should be negligible, as has been shown in this series.

5. *Subsequent obstetric difficulty.* Huber (1939) followed up 100 cases and found that this was not demonstrably increased following Dührssen's incisions. I have traced only 8 patients; 4 have become pregnant and have had spontaneous deliveries.

6. *Foetal mortality.* Douglass and Graves (1948) reported a mortality of 17·2 per cent, but Abrams (1936) reported 36 cases with 2 stillbirths, both craniotomies for hydrocephalus, and 1 neonatal death, a baby with multiple congenital deformities. Corbett (1952) reported a series of 24 cases with a foetal mortality of only 4 per cent. In my small series there was no perinatal mortality or morbidity, and it is considered that, with a careful choice of case, the foetal mortality should be very low.

Operative Technique

The greatest diameter of the head must have passed the cervico-vaginal junction. The incisions should be placed at 9 o'clock and 3 o'clock where there is minimum tension, and should be repaired.

In all except 1 the forceps were applied before the cervix was incised. In those in which the occiput was in a lateral or posterior position, manual rotation was performed before the forceps were applied. In one case it was necessary to incise the cervix before manual rotation could be effected and, in such a case, it is important to effect the rotation and application of forceps with the utmost gentleness, in order to avoid extending the incision by pushing a hand or blade into the apex, and to avoid upward displacement of the head during rotation.

Intravenous ergometrine 0·25 mg. was given, when the anterior shoulder was born, and the placenta was expelled spontaneously in all cases except 1, in which a manual removal was necessary.

The incisions were repaired with figure-of-eight catgut sutures, the top bite being placed above the apex of the incision. With the apex at the cervico-vaginal junction this is quite safe; above this level, however, it would be necessary to bear in mind the position of the ureter and main uterine vessels.

The flaps were held in light-weight ring forceps, and the needle inserted at least ⅛ inch from the cut edge, in order to get good apposition of all layers and prevent the stitches from cutting out. The stitches were tied without tension to avoid strangulation of the edges.

Indications for Cervicotomy

The operation is indicated when the greatest diameter of the head has descended below the cervico-vaginal junction and early delivery is required, the only obstacle being the undilated cervix. In this series the operation was performed for (1) foetal distress, (2) prolapse of the cord, (3) prolonged labour due to weak uterine action. A fourth indication is cervical dystocia.

1. *Foetal distress.* In 1 case the foetal heart dropped below 80 and failed to recover between pains. The baby was delivered within 10 minutes of this observation being made. It was shocked at birth, but soon recovered, and it is felt that only this operation could have saved it.

2. *Prolapsed cord.* The only case was a breech presentation with flexed legs. The cord prolapsed when the cervix was 7 cm. dilated, and a waiting policy was adopted as the cord pulsations and foetal heart were satisfactory. Within a few minutes marked slowing of the foetal heart occurred, and the breech was extracted. As anticipated, the head was held up by the cervix. Forceps were applied, and the cervix was incised at 9 o'clock and 3 o'clock, after which delivery was quite easy.

3. *Prolonged labour due to weak uterine action.* In 7 cases the decision to deliver was made

because the patient was becoming tired, and labour had been in abeyance for at least 12 hours. Delivery was effected before frank maternal distress appeared, as to await this is to court disaster.

Jeffcoate and Lister (1952) point out that slow dilatation of the cervix is due either to incoordinate or weak uterine action, or abnormal resistance of the cervix. They state that in the former "the cervix tends to remain thick and incompletely effaced . . . It is the internal os rather than the external os which is not dilating. Cervical dystocia, however, is recognized by the finding of a low presenting part fitting snugly on to a thin cervix fully effaced, and with an external os appearing as a tight ring with a sharp edge." In the latter type of case, when the cervix is half dilated, they consider that cervicotomy is easy, safe, and satisfying.

Whilst agreeing with Jeffcoate and Lister's remarks on cervical dystocia, one cannot agree that weak uterine contractions are necessarily associated with a cervix that remains thick and incompletely effaced, though of course, cases of this kind occur and are unsuitable for cervicotomy.

Not one of the 7 cases under consideration was clinically a cervical dystocia. There was no question in any of them of the cervix resisting the powerful dilating force of a normally acting uterus.

Halliday and Heyns (1952), following some beautiful experimental work, propose that there is an almost uniform muscular activity over the whole of the uterus in labour, and that this causes a hydrostatic pressure within the uterus, and a dilatation of the cervix according to straightforward mechanical principles. They thus introduce the conception that dilatation depends on power rather than polarity.

There is undoubtedly some dystocia due to the fibrous nature of the inner major part of the cervix in all primigravid labours, which a normally acting uterus overcomes, but only by tearing the cervix in nearly 60 per cent of cases.

In this group of prolonged labours, the reason for slow dilatation was weak uterine action, and we consider that, if the uterus had acted normally, the cervices of at least 60 per cent of them would have torn at the lateral commissures, and that by incising the cervix we were assisting nature to perform a normal function. There thus seems to be a logical basis for cervicotomy in certain cases of weak uterine action.

4. *Cervical dystocia.* There were no cases in this series, but Jeffcoate has clearly pointed to the value of cervicotomy in this condition, though I feel it could be safely done with much less than half dilatation.

Summary

(1) The cervix was seen to be torn in 90 (58 per cent) of 155 consecutive primigravid deliveries. The tears were at 3 o'clock or 9 o'clock or both in 71, and at 6 o'clock in 19. These were never in the anterior half of the cervix.

(2) Thirteen cases of cervicotomy without maternal or foetal mortality or morbidity were described.

(3) The hazards and mechanics of cervicotomy were considered and, in the light of these and the above series of cases, an attempt was made to define the use and limitations of the operation and a technique described.

Acknowledgments

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ACUTE IDIOPATHIC PORPHYRIA COMPLICATING PREGNANCY

BY

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ACUTE porphyria is a comparatively rare disease which in recent years has attracted considerable attention. Some 300 cases have already been reported (Hirson, 1953), the majority being from Scandinavia and America. Though the disease is more common among females, often giving rise to acute abdominal pain, constipation, vomiting and amenorrhoea, and resembling ectopic pregnancy or other pelvic conditions, it has received scant mention in obstetrical and gynaecological literature and many gynaecologists may be unaware of its existence.

Porphyria is defined as a metabolic dysfunction due to an inborn error of porphyrin metabolism (Calvy, 1950). The porphyrins, which are red pigments, are normal constituents of haemoglobin, myoglobin and chlorophyll, and are believed to play a fundamental role in cellular metabolism. Their biochemistry has been extensively studied, but it suffices to say that they have a basic structure of 4 pyrrole rings, containing 8 replaceable hydrogen atoms. When porphyrins are produced in excess, they are excreted in the urine as uroporphyrins or coproporphyrins, or as the colourless chromogen porphobilinogen. The relationship of porphyrins to porphyria has been compared with that of uric acid to gout, the porphyrinuria being merely the sign of a more deeply rooted metabolic disorder (Linder, 1947). The disease tends to be familial and is believed to be transmitted according to Mendelian laws.

Two chief forms occur.

(a) *Congenital.* This is characterized by undue sensitivity to light and the deposition of pigment in bones and teeth. It usually affects young boys, and their urine contains uroporphyrin I.

(b) *Acute or Idiopathic Porphyria.* This, by far the more important form of the disease, usually affects young adult women. It is sometimes divided into classical, nervous, toxic, and comatose varieties. A chronic or "mixed" type has also been described which combines some of the features of both the congenital and acute forms.

In the typical case, idiopathic porphyria manifests itself by attacks of abdominal pain, vomiting, stubborn constipation, and red or brown discoloration of the urine. However, the urine may remain unpigmented even during an acute attack. Occasionally, the patient may exhibit a peculiar psychical condition, closely resembling hysteria, and may be labelled a neurotic or referred for psychotherapy. Menstrual disturbances, particularly amenorrhoea, are common during acute attacks (Nesbitt, 1944; Goldberg, MacDonald and Rimington, 1952), a matter which has special significance for the gynaecologist. In a proportion of cases, the nervous system becomes involved, leading to muscular weakness and occasionally to a lower motor neurone type of paralysis which is nearly always fatal.

Spontaneous remissions often occur and the disease may remain latent for years, acute attacks being precipitated by trauma, infection, indulgence in alcohol, and certain drugs, especially the sulphonamides and barbiturates. Because of their symptoms, many porphyrics take a variety of patent medicines and doctors' bottles and in consequence may become drug addicts.

It is with good reason that acute porphyria has been dubbed "The Simulator", for a multitude of bizarre symptoms can occur affecting the gastro-intestinal and nervous systems, often causing serious difficulty in diagnosis. The disease has a special tendency to mimic the "acute abdomen", even showing muscle guarding or rigidity, and it is not surprising, therefore,

how often these patients come under the surgeon's scalpel. Hoagland (1942) estimated that one-third of all cases are operated on as acute abdominal conditions, common misdiagnoses being appendicitis, ectopic pregnancy, and acute intestinal obstruction due to a tumour. In some of the reported cases the "tumour" has proved to be the caecum distended with hard faeces (Calvy, 1950).

The exact causes of the symptoms are still somewhat in doubt. The discoloration of the urine is caused by the increased excretion of pigments; the crampy pains and constipation are believed to be due to spasm of smooth muscle, while the nervous symptoms probably reflect a direct toxic action of porphyrins on nervous tissue. The gross depletion of serum electrolytes is usually attributed to vomiting, though Linder (1947) believes that there is functional adrenal insufficiency in some cases, while Davies (1949) lays the blame on renal damage.

Once the condition is suspected, diagnosis is then an easy matter. The combination of recurring crises of acute abdominal pain, stubborn constipation, passage of dark red urine, nausea, and hysterical outbursts is almost pathognomonic of the disease, and porphobilinogen can be demonstrated in the urine by relatively simple tests, such as that described by Watson and Schwartz (1941).

In the absence of precise knowledge of the fundamental metabolic disorder which is at the root of the disease, treatment can be only symptomatic and supportive. Opiates may be used to relieve pain during acute attacks, constipation must be dealt with, and attention paid to fluid and electrolyte balance. There is often vitamin deficiency and evidence of liver damage, and it is rational to administer nicotinic acid and riboflavin, together with liver extract. Eucortone and A.C.T.H. have been employed on the assumption of a functional adrenal insufficiency, but the results have been equivocal (Linder, 1947; Abrahams, Gavey and Maclagan, 1947; Goldberg *et al.*, 1952). Gilhespy and Smith (1954) have recently reported a favourable response to neostigmine injections in a patient who was emaciated, with profound muscle weakness. Self-medication with barbiturates and sulphonamides, or abuse of alcohol, must be guarded against as they definitely cause harm. Likewise, a too-hasty resort to surgery may have disastrous consequences. Dean (1953) who has attended no less than 12 cases, 3 of whom died after operation, states that paralysis and death are especially prone to follow thiopentone anaesthesia. Waldenström (1937) estimates that about 50 per cent of patients eventually succumb to the disease, while the death-rate rises to 80 per cent if there is involvement of the central nervous system.

Case Report

The patient, a slightly-built young woman, aged 23, was referred by her doctor to the hospital antenatal clinic on 31st July, 1953, with a diagnosis of tubal pregnancy. She had been married for 4 years and this was her first pregnancy. She had had her appendix removed 8 months previously. The last menstrual period had begun on 15th June and she had felt well until one week before attending the clinic, when a sudden attack of lower abdominal pain and vomiting had occurred. The vomiting had quickly abated but she still experienced frequent shooting pains in the right iliac fossa and thigh, together with a constant ache in the lumbar region. There was constipation and frequency of micturition but no dysuria. Three days before attending the clinic there had been slight painless vaginal bleeding, lasting only for a few minutes.

On examination, there was some tenderness and muscle "guarding" in the right iliac fossa. The blood-pressure and urine findings were normal. The uterus was found to be bulky and soft and marked tenderness was elicited on pressure in the right lateral vaginal fornix though no mass was felt. As a tubal pregnancy was suspected, she was admitted to hospital for observation.

Three days after admission (3rd August) she again complained of acute stabbing pain in the right iliac fossa and back, with frequency and pain on micturition. She appeared to be cyanosed and her blood-pressure had risen to 160/90. (Similar cyanosis has been noted by Turner (1938) and by Goldberg *et al.* (1952).) There was still definite tenderness in the right iliac fossa and also in the right renal area, but muscle-guarding was now absent. A tentative diagnosis of renal colic was made. Pethidine was administered with a good effect.

The results of various pathological investigations were as follows: haemoglobin, 14·1 g. per cent (95 per cent); leucocyte count, 10,200 per cubic millimetre; erythrocyte sedimentation rate (observed), 35 mm. in one hour; erythrocyte sedimentation rate (corrected), 26 mm. in one hour; packed cell volume, 41 per cent; blood urea content, 21 mg. per 100 ml.; blood group, A Rhesus positive; Wassermann reaction, negative; urine examination, nil abnormal discovered.

On 5th August, further slight vaginal bleeding took place. She was still constipated and complaining of pain

in the right iliac fossa as before. Vaginal examination now revealed a tender ill-defined mass to the right of the uterus, and as it was not possible definitely to exclude an ectopic pregnancy it was decided to perform a laparotomy. On opening the abdomen, the caecum and colon were found loaded with hard faeces, while the pelvic organs appeared normal. The uterus was the size of 10-weeks pregnancy. The patient's convalescence was uneventful. Her constipation responded to frequent enemas and aperients, and she was discharged free from pain on 24th August.

The patient was re-admitted on 2nd October, suffering from "hyperemesis". During the preceding few weeks she had become listless and apathetic, and suffered from frequent vomiting and hiccups. The attacks of crampy abdominal pain, backache, and urinary frequency had again appeared and her doctor had noticed "blood" in the urine on 2 occasions. The patient was now extremely thin and was again very constipated. Her blood-pressure was normal but the urine contained a trace of albumen. Microscopy and culture of the urine and intravenous pyelography revealed no abnormality. However, 2 foetal spines were visible on the X-ray plate. She was given enemas, a mainly fluid diet, and barbiturates and her condition gradually improved. Three days after admission, for the first time in hospital, the urine was noted as being dark-brown in colour. However, the significance of this finding was not appreciated at the time. The patient was discharged on 12th October, by which time she was taking a normal diet and her symptoms had again disappeared.

On 6th November she was again admitted (3rd time) at her doctor's request. Once more she was complaining of pain, this time in her legs and arms, and also she experienced weakness in her limbs, which made housework and even walking difficult to accomplish. She admitted to being a prey to morbid fears and her husband stated that she had had 2 hysterical attacks a few days before entering hospital. There had been no vomiting or urinary symptoms on this occasion. The patient appeared emaciated and emotional. Muscle tone was poor and there were multiple bruises on both legs. Knee and ankle reflexes were absent. The uterus had enlarged considerably and a further X-ray showed 2 normal foetuses.

The clinical findings now suggested peripheral neuritis, due to vitamin deficiency. Accordingly, treatment was begun with large doses of the vitamin B complex, and she was kept lightly sedated with barbiturates. However, her general condition remained poor, she was now quite confused and threatened to commit suicide on one occasion.

The possibility of porphyria was now considered for the first time and examination of the urine quickly revealed the true diagnosis. The test for porphobilinogen was positive, while the fluorescence test under ultraviolet light and spectroscopic examination showed the presence of uroporphyrin. Injections of liver extract and vitamin B were given, together with pethidine to relieve the pain, and her condition slowly began to mend. Though her limbs were so painful and weak at first, by the beginning of December she was walking unaided and was allowed to leave hospital on 10th December. From this date onward, she was free from symptoms though the urine still contained porphyrins and was occasionally pigmented.

Confinement. She was admitted in labour on 31st January, 1954, when 32-weeks pregnant and was delivered normally of twins, a girl weighing 2 pounds 15 ounces and a boy 2 pounds 10 ounces. Both babies survived. No porphyrins were found in the babies' urine nor in that of the patient's immediate family. The puerperium was uneventful and she was discharged on the 10th day. Now, 12 months later, porphyrinuria is still present, but she remains free from symptoms.

Discussion

This case illustrates vividly the way in which acute porphyria can mimic many diverse conditions and lead to diagnostic confusion. During the early months of pregnancy, ectopic gestation, renal colic, hyperemesis gravidarum, hysteria, and polyneuritis were successively diagnosed, and it was not until the urine was tested for porphyrins that the disease was finally discovered. Unfortunately, in the meantime, the patient had been subjected to laparotomy and barbiturates had been prescribed liberally. The deleterious effects of barbiturates are well known, and Calvy (1950) has stressed the dangers of ill-advised laparotomy during the acute phase of the disease, when "the combination of preoperative sedation and trauma may cause progression of symptoms and a rapidly fatal termination".

Early diagnosis is therefore of vital importance, for the doctor in his efforts to assuage the aches and pains of an apparently neurotic woman, or actuated by an excess of surgical zeal, may himself be the unwitting cause of his patient's death. The main difficulty in the early recognition of acute porphyria lies in its comparative rarity, so that the diagnosis will only be made if it is borne in mind as a possibility when a patient has vague symptoms referrable to the gastro-intestinal tract, pelvis, or nervous system, together with emotional instability or pigmented urine.

Four other instances of porphyria complicating pregnancy have been reported in the literature. The first of these (Linas, Solomon and Figge, 1947) was one of chronic or "mixed" porphyria, and the patient exhibited cutaneous

vesicles and pains in the limbs. She was delivered of a live child, and afterwards her condition rapidly improved.

Rawlings (1950) has reported a case with the classical features of acute intermittent porphyria in which pregnancy occurred one year after the discovery of the disease. Pregnancy and labour were normal and 2 years later the patient was free from symptoms though the urine remained pigmented.

In the case reported by Coleman (1948), the patient was seriously ill during the first trimester, but then rapidly improved and had a normal child by Caesarean section. Nine months after her confinement the patient remained well.

Freedman, Yeagley and Brooks (1952) have described a similar case, in which pregnancy occurred during a brief intermission in the course of the disease. During the first few weeks, the disease progressed alarmingly, and motor and respiratory paralysis developed which necessitated emergency tracheotomy. However, an improvement then set in and the patient remained well for the duration of pregnancy. Two years afterwards, she was still free from symptoms.

Spontaneous remissions and exacerbations are common in porphyria, and it is therefore difficult to assess the effects, for good or ill, of pregnancy on the course of the disease. However, the result in this case, and the reports of the other 4 cases previously described, give some grounds for believing that the total experience of child-bearing may have a beneficial effect on the porphyric patient. The stimulus of pregnancy upon the endocrine system, and especially upon the anterior pituitary, is well recognized, and it may be that the increased pituitary action can offset the degree of functional adrenal insufficiency which is thought to be partly responsible for the clinical expressions of porphyria.

Summary

An obscure disease, acute idiopathic porphyria, can present a wide range of symptoms affecting the gastro-intestinal tract, pelvic organs, and nervous system.

Surgical interference and various drugs, including the barbiturates and sulphonamides, are exceedingly dangerous during acute attacks.

The condition may pose serious diagnostic problems for the abdominal surgeon or gynaecologist, and though it is uncommon, it surely deserves some mention in surgical and gynaecological textbooks.

A case is described where the disease occurred during pregnancy, simulating ectopic gestation, renal colic, hyperemesis gravidarum, hysteria, and polyneuritis.

Reference is made to 4 similar cases already reported in the literature.

I wish to thank Mr. F. J. Burke for his helpful encouragement and for permission to publish the case record.

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PREGNANCY COMPLICATED BY IMPERFORATE ANUS WITH CONGENITAL RECTO-VAGINAL FISTULA

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ABNORMALITIES in the anatomy of the anus are often accompanied by fistulous communications between the rectum, bladder, urethra or vagina. A recto-vaginal fistula is the most common error of the group and as a rule the opening is at the lower end of the recto-vaginal septum, but it may occur in the vulvar region (vestibular anus) or the upper part of the vagina. Rarely, the rectum may communicate with the uterine body or cervix.

In cases of imperforate anus associated with a recto-vaginal fistula there is no immediate danger to life at birth as faecal drainage through the fistula is satisfactory and the condition may even escape unnoticed until later life.

CASE REPORT

The patient was a healthy primigravida aged 38 years who was referred to the hospital antenatal clinic in April, 1954. She was then 32-weeks pregnant and her general condition was satisfactory. She stated that as a child she had been told that her "bowel was twisted" but she was not aware of the true nature of the deformity.

On vaginal examination, the absence of the anus was discovered and the skin over this area showed no depression or dimpling. The external appearances of the vulva were normal (Fig. 1). The rectum was found to open into the posterior wall of the vagina about one inch above the margin of the hymen. The introitus was tight and further detailed examination was not made at this time. The vagina appeared healthy and there was no evidence of vaginal discharge.

She was admitted to hospital in the 38th week of the pregnancy for further detailed examination to decide the best method of delivery. An examination under anaesthesia was made on 14th June, 1954. There was a thick band running antero-posteriorly at the hymen which required ligation and excision. The congenital recto-vaginal fistula admitted one finger. There was no independent sphincter and bowel control had obviously depended on the efficiency of the pelvic floor muscles. The pelvic measurements were entirely satisfactory, the outlet was of wide dimensions, the antero-posterior diameter being increased by the congenital absence of the coccyx and lower end of the sacrum.

X-ray pelvimetry. The lateral view showed absence of the coccyx and lower part of the sacrum. The ischial spines were absent. The shape of the pelvic brim and the measurements were normal (Fig. 2).

On 15th June, 1954, an elective lower uterine segment Caesarean section was done under general anaesthesia. A healthy male child weighing 7 pounds and 6 ounces was delivered. The puerperium was uneventful, there was no rise of temperature or pulse rate, nor any sign of genital tract infection. She was dismissed well with her baby on the 15th day after operation.

DISCUSSION

Imperforate anus has been classified into 4 types by Ladd and Gross (1934) and the abnormality in this patient was of type III with in addition a congenital recto-vaginal fistula which is present in 93 per cent of such cases (Santulli, 1952). Operative correction may be attempted in childhood, but the majority are against operation if the bowel control is reasonable. On further questioning the patient stated that she had reasonably good bowel control providing that the faecal matter was well formed, and by adjusting her diet to encourage constipation she had been able to lead a comparatively normal life. In adolescence, surgical repair of the deformity had been considered but as bowel control was reasonable a difficult and often unsatisfactory operation was thought to be unjustified.

The main problem in this case was whether or not to allow vaginal delivery. As examination showed no evidence of an independent sphincter, it was felt that any damage or stretching of the

pelvic floor muscles would lead to incontinence of faeces, with perhaps permanent loss of bowel control, and accordingly Caesarean section was preferred.

There have been few reports of similar cases in the literature. Potts (1932) reviewed 8 cases and considered that the patient suffers the risks of post-partum infection as well as the late results of lacerations with loss of sphincter control. Hipsley (1925), Packard and Kirshbaum (1932), Moore and Lawrence (1952), and Powell and Lowden (1953) have reported single cases and they all employed Caesarean section to prevent any damage to the pelvic floor muscles. The risk of infection after operation does not appear to be high. In the case reported by Powell and Lowden (1953) the vagina was full of faeces but post-operative recovery was uneventful. Robertson (1949), in describing 2 cases in children that he operated on successfully, emphasized the healthy state of the vaginal mucosa and the absence of infection. In the present case, the vaginal mucosa had remained remarkably healthy and there was no sign of infection in the post-operative phase.

Summary

(1) A case of pregnancy complicated by imperforate anus and recto-vaginal fistula is described.

(2) Caesarean section is considered to be the safest method of delivery.

We wish to thank Dr. John Hewitt for permission to record this case.

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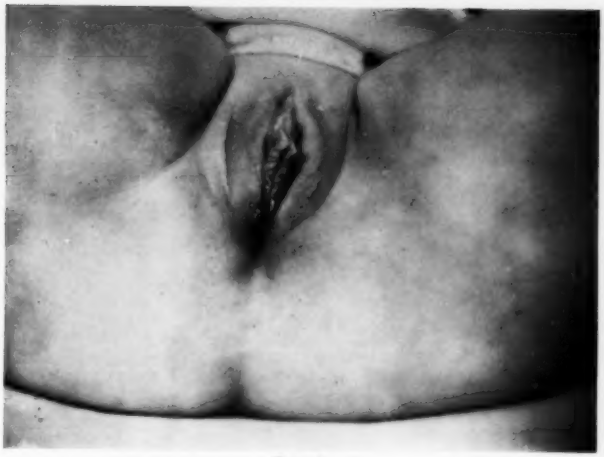

FIG. 1

The external appearance of the deformity. The anus is absent and the skin over this area shows no depression or dimpling.

FIG. 2

Lateral X-ray of the pelvis showing the absence of the coccyx, the rudimentary sacrum, and the absence of the ischial spines.

MASSIVE BLEEDING INTO THE AMNIOTIC SAC IN A CASE OF ACCIDENTAL HAEMORRHAGE (WITH A LIVE BABY)

BY

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A LARGE haemorrhage into the amniotic sac appears to be a very rare occurrence in the course of an accidental haemorrhage. Rarely does an accidental haemorrhage rupture into the amniotic sac, and seldom do these cases result in the delivery of a live baby.

CASE REPORT

Mrs. J.H., aged 29, a para-4, was admitted as an emergency on 5th January, 1954, because of an ante-partum haemorrhage 3 weeks from term. Her previous obstetric history showed that she had had 4 easy normal deliveries, over the past 7 years, of healthy babies varying in weight from 7 to 9 pounds each. Her health had always been excellent.

The present pregnancy had progressed satisfactorily until the 3rd month, when she threatened to abort, but after one week in bed the bleeding ceased and the pregnancy continued without any further complications. Three weeks before term, on 5th January, 1954 (the day of admission to hospital), she experienced backache and painless uterine contractions. The latter then became painful and she thought labour had begun. A few hours after the onset of labour pains a profuse vaginal haemorrhage occurred, and it was estimated by the midwife in attendance at her home to be about a pint of blood plus some liquor. She was sent into hospital shortly afterwards.

On admission to hospital the patient's general condition was found to be very good, the bleeding having almost ceased shortly after the first profuse loss. She presented as a well-built woman, about 12 stones in weight, with no obvious signs of severe blood loss. She was flushed and apprehensive, with a pulse of 90 per minute and a blood pressure of 120/60. Abdominal examination revealed a soft, non-tender uterus at term. The presentation was an L.O.A. with the head very high. The foetal heart was present and normal. Inspection of the vulva revealed a slight active loss of dark red blood.

Venepuncture was performed and a specimen of her blood collected for grouping and cross-matching two pints of donor's blood.

It was concluded that the case was probably one of placenta praevia and preparations were made to examine her per vaginam under anaesthesia in the theatre, with a view to the performing of Caesarean section if necessary. Under light general anaesthesia (N_2O, oxygen and Trilene) a speculum examination showed the cervix to be situated high up in the vagina and about 3-fingers dilated with a smooth, dark purple coloured mass protruding through it. On first impression this mass was thought to be the placenta, but on further digital examination it was felt to be only soft membranes. An attempt was then made to explore the lower uterine segment for the presence of a placenta praevia. This was not felt but, during the examination, the forewaters ruptured and about a pint of almost pure blood gushed out. With fundal pressure, suprapubic and vaginal manipulations, the vertex was pushed down into the pelvic inlet, and the vaginal bleeding was controlled. The foetal heart, after slowing considerably as a result of these manœuvres, regained its normal rate and rhythm within a few minutes.

Vaginal bleeding having ceased, the patient was returned to the labour ward to await a normal delivery. Some 20 minutes later, the patient having recovered from the effects of the anaesthetic, an intravenous Pitocin drip (15 units of Pitocin in 1 litre of glucose-saline solution) was set up. Strong uterine contractions commenced almost immediately and one hour later the patient was delivered spontaneously of a live 7 pounds female baby. The infant was covered in blood and the skin was deeply blood-stained. The naso-pharynx and the stomach were aspirated and a few ounces of almost pure blood were recovered from the latter.

Normal respirations became established 5 minutes after delivery and the baby was soon crying lustily. Fifteen minutes after delivery the baby passed a large melaena stool of dark blood clots.

The placenta and membranes were delivered 5 minutes after the baby and were found to be complete except for a very ragged area at the fundus of the amniotic sac. On careful examination the hole in the membranes, through which the baby had been delivered, was found to be at least 5 inches from the lowermost edge of the placenta. At this edge a battledore insertion of the cord was present. The upper edge of the placenta showed evidence of ante-partum separation, with some old blood clot adherent on its surface. The membranes adjacent to this area of placental separation were very ragged and torn,

as if the escaping blood from the accidental ante-partum haemorrhage had burst its way through the membranes into the amniotic sac. The amnion was also deeply stained with dark blood pigment.

The baby, after coughing up a little more dark blood, made an uninterrupted recovery. The mother's haemoglobin estimation 3 days after delivery was 60 per cent, and oral iron was prescribed. Both mother and child were discharged home on the 10th day after delivery.

Comment

On analyzing this case it appears that a non-toxic accidental haemorrhage occurred, causing a separation of the upper edge of the placenta. The subsequent retroplacental haemorrhage ruptured into the amniotic sac and shortly afterwards some blood plus some liquor tracked down between the membranes and the uterine wall, to appear vaginally as a profuse ante-partum haemorrhage. The foetus (still *in utero*) inhaled and swallowed a quantity of the blood now in the amniotic cavity while it was probably in a state of distress.

After delivery the baby showed definite signs of having been immersed in blood for many hours ante-partum, as its skin was deeply blood-stained. In addition, the passage of a large melaena stool soon after delivery substantiated the claim that the amniotic cavity contained much blood for some hours before delivery.

No other signs of haemorrhagic disease of the newborn were seen. Reconstitution of the placenta and membranes confirmed the above conclusions.

Summary

(1) A case of non-toxic accidental haemorrhage with massive rupture into the amniotic sac has been described.

(2) A live baby, showing signs of having been immersed in blood for some hours before delivery, was born.

(3) Examination of the placenta and membranes substantiated the previous conclusions.

(4) Both mother and baby are alive and well.

I would like to thank Mr. Wigley for permission to publish this case.

RUPTURE OF THE VAGINAL VAULT WITH EVISCERATION FOLLOWING VAGINAL HYSTERECTOMY

BY

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COMPLETE rupture of the vaginal vault with extrusion of bowel has occasionally been recorded as a complication of vaginal hysterectomy. In the following case such an accident occurred two and a half years after the operation.

CASE HISTORY

Mrs. F.T., aged 83 years, was admitted to the Birmingham and Midland Hospital for Women as an emergency admission at 11 a.m. on 8th January, 1953. On the previous evening (7th January) the patient had been vaguely unwell and very tired. After supper she felt sick and vomited. Immediately following this she felt a desire to defaecate and on going to stool felt a large swelling come down in the region of the vulva. At the same time she experienced pain in the hypogastrium. She managed to get to bed with assistance and lay fully clothed all night. She experienced no further pain; did not vomit and slept intermittently. The patient's doctor, summoned in the morning, found her lying in bed with coils of bowel protruding from the vulva, some actually lying beneath the buttocks and thighs. Without any interference she was transferred to hospital.

Previous history

The patient had had 3 normal confinements and 3 miscarriages. The menopause occurred at 50 years of age. In July, 1950, a vaginal hysterectomy had been performed on account of uterine prolapse. The operation and convalescence had been uneventful and had resulted in complete cure of her symptoms. During the previous few months, however, she had sometimes felt that there was a recurrence of swelling in the vaginal region, relieved on lying down.

On admission the patient's general condition was remarkably good. Her pulse rate was 104 per minute and blood pressure 150/90 mm. of mercury. A Ryle's tube was passed and atropine sulphate 1/75th grain (0·9 milligrammes) was given intravenously. She was immediately transferred to theatre where anaesthesia was induced with 0·15 gramme of sodium thiopentone and maintained with gas, oxygen and ether. The patient's underclothes were cut off while the extruded loops of bowel were held in a large gauze saline pack. Toilet was performed with 1 per cent "Cetavlon" (cetyl-trimethyl-ammonium bromide) solution and the bladder emptied by catheter. On detailed examination it was found that approximately 2 feet of small bowel was outside the vulva. The bowel was oedematous and congested and a portion 6 inches in length was extremely dark blue in colour, though retaining its lustre. On digital exploration a small annular opening, about 2 centimetres in diameter, was felt in the vaginal vault through which the gut had prolapsed.

After applying penicillin and sulphathiazole powder to the exposed bowel it was slowly reduced by taxis over a period of 20 minutes. After trimming the edges with scissors, the vaginal vault was closed with interrupted catgut sutures. A gauze vaginal pack was inserted.

Post-operative progress

Morphine sulphate 1/4 grain (16 milligrammes) was given 4-hourly for 36 hours. Gastric aspiration was continued and fluids were given by the intravenous route. In view of the certain peritoneal infection, penicillin 100,000 units 4-hourly and streptomycin 0·5 grammes were administered twice daily for 7 and 10 days respectively.

The patient made a most remarkable recovery considering her age. The temperature did not rise above 99 degrees Fahrenheit. She developed only a mild degree of post-operative abdominal distension. Bowel sounds were heard the day following operation and flatus was passed following an enema on the second day and regularly thereafter. The pack was removed after 36 hours. Intravenous infusion was continued for 4 days and gastric aspiration for 5. A peripheral neuritis affecting both lower limbs proved a troublesome complication during convalescence but responded slowly to physiotherapy. She was eventually discharged on 27th February, 1953.

When seen 2 months later she was free from symptoms and the result of the emergency repair of the vault seemed perfectly satisfactory.

DISCUSSION

Considering the frequency of the operation of total hysterectomy (vaginal or abdominal) it is in many ways remarkable that catastrophes such as the one described do not occur more fre-

quently. Beebe and Edwards (1951), in a review of lesions of the vaginal vault following complete hysterectomy, record 2 cases of prolapse of small bowel through the vault following vaginal hysterectomy. They cite Cullen as having noted, in his discussion of the causes of death following vaginal hysterectomy, that such a complication had been observed about the turn of the century. Eight cases were mentioned but some of these were associated with adhesion of bowel to the vault followed by faecal fistula formation. Kennedy and Campbell (1944) state that they have had no experience of prolapse of intestine following vaginal hysterectomy. They do record 2 cases of prolapse of omentum occurring as a fairly early complication of the operation. Prolapse of a Fallopian tube has frequently been observed but is of little clinical importance. Recently Kayser, Heaney and Dahleen (1951) and Outerbridge (1953) have recorded cases very similar to the present one. In each instance vaginal hysterectomy had been performed in an elderly patient for prolapse and each had developed a recurrence of the condition within a year; a "high rectocoele" in one and a recto-enterocoele in the other. In the first instance rupture followed a bout of coughing. In the second the patient "took an enema and was expelling it when she was summoned to the telephone". On rising quickly she felt the bowel come down between her legs.

In the case described it seems certain that the same combination of two factors were concerned. Firstly, some recurrence of vault prolapse or enterocoele followed by a factor raising intra-abdominal pressure, in this case a gastro-intestinal upset with vomiting. In the discussion following the original presentation of this case,* Mr. S. W. Maslen-Jones, Wolverhampton, described a similar case in which the rupture was precipitated by intestinal obstruction.

As observed by Beebe and Edwards, the incident seems to be predominantly a complication of vaginal rather than abdominal hysterectomy. The latter operation is less frequently performed in cases with prolapse. Following total removal of a uterus lying at its normal level in the pelvis, any raising of intra-abdominal pressure will tend to force the anterior and posterior walls in apposition, putting no strain on the vault scar. If, however, there is vault prolapse or if the vagina has been so shortened that the anterior and posterior walls cannot come into direct apposition, most of the strain will fall on the scar. This latter occurrence is much more likely following the vaginal operation.

At the original operation, a plastic tube drain had been inserted directly through the vaginal vault into the peritoneal cavity and removed 48 hours later. It is impossible to exclude this as a relevant factor but, as has been observed (Kennedy and Campbell, 1944), many operators employ a similar procedure in both abdominal and vaginal hysterectomy, apparently without this complication occurring.

Summary

A case is recorded of rupture of the vaginal vault with extrusion of small bowel, occurring as a late complication of vaginal hysterectomy.

In association with shortening of the vagina or recurrence of vault prolapse, any raising of intra-abdominal pressure may produce rupture should the vault scar be at all weak.

I wish to thank Mr. P. J. Ganner, F.R.C.S., F.R.C.O.G., for permission to publish this case.

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* At the Birmingham and Midland Obstetrical and Gynaecological Society on 18th March, 1953.

SUCCINIC DEHYDROGENASE AND ENDOGENOUS REDUCTASE ACTIVITY IN THE RABBIT OVARY IN PREGNANCY*

BY

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THIS report is concerned with localization of sites of succinic dehydrogenase and endogenous reductase activity in the ovary of the rabbit during pregnancy. Correlation has been shown between sites of cell growth and function in various contexts and sites of activity of the dehydrogenase enzyme group, succinic dehydrogenase in particular (Padykula, 1952). In the human (Foraker, Aguilar Celi and Denham, 1953), rabbit (Foraker and Denham, 1952; Foraker, Denham and Mitchell, 1953) and rat (Padykula, 1952) ovary, evidence of dehydrogenase activity has been found to correlate to some degree with sites of cell proliferation and presumed hormone production. Padykula (1952) has stated that the distribution pattern of succinic dehydrogenase suggests that this oxidative enzyme is in greatest concentration within those portions of tissues and organs which show high metabolic activity, or are engaged in absorptive or secretory activity.

Extensive biochemical investigations of succinic dehydrogenase were in the past largely concerned with the activities of this enzyme in entire tissues and organs, and not with its exact cellular distribution (Padykula, 1952). In recent years, histochemical methods for the demonstration of succinic dehydrogenase have provided means for determining its sites of activity within cells and tissues (Padykula, 1952; Seligman and Rutenburg, 1951). The principle of the demonstration is the observation of the change in colour of a suitable hydrogen acceptor (one of the various tetrazolium salts) when it is reduced by the enzyme in the presence of a suitable substrate (Gomori, 1952a). Endogenous reductase is manifested by the positive tissue reaction induced by the presence of various endogenous substrates in the tissues (Gomori, 1952a). For specific succinic dehydrogenase demonstration, this endogenous activity is destroyed by freezing the tissue (Shelton and Schneider, 1952), then succinate in excess is added as a substrate for the reaction (Foraker and Denham, 1953a).

It seemed of interest to determine sites of activity of this enzyme group in the ovary during pregnancy. At this time the ovary is subject to considerable morphologic and physiologic change. It is both the initiator and the recipient of hormonal stimulation (Meyer and McShan, 1950). The ovary in pregnancy should afford an excellent testing ground for the postulation that the distribution of sites of succinic dehydrogenase activity may correlate with certain types of cell function, such as hormone production. In addition, such demonstration should constitute a contribution of intrinsic interest to our knowledge of the growth, histology, histochemistry and function of the ovary.

* Read at the meeting of the Histochemical Society, Atlantic City, N.J., 17th April, 1954.

This investigation was supported by Research Grants C-1486 C and C 2111 from the National Cancer Institute, of the National Institutes of Health, U.S. Public Health Service.

In the present series of mid-gestational rabbit ovaries, evidence of succinic dehydrogenase and endogenous reductase activity was marked in many of the cell elements. There was little evidence of correlation of this activity with lipid, alkaline phosphatase or glycogen.

Materials and Methods

Twenty-seven New Zealand or California strain rabbits having a gestation period of 30 to 32 days were employed. On the twelfth or thirteenth day of gestation, the animals were sacrificed. Ovarian tissue was fixed in Zenker's fluid, ice cold acetone, neutralized formalin, Rossman's fluid (Wislocki and Dempsey, 1948), and incubated in neotetrazolium (Foraker and Denham, 1952). Frozen sections (15μ) of the formalin fixed tissue were stained with Sudan IV (haematoxylin counterstain) and Sudan black B (Bismarck brown R counterstain) to demonstrate lipid (Lillie, 1948a). Sections from the acetone fixed blocks were processed for alkaline phosphatase demonstration (Gomori, 1952b). Sections (5μ) from the Rossman's fluid fixed tissue were subjected to the periodic acid-Schiff technique (Lillie, 1948b) for the demonstration of glycogen. Control sections were saliva digested (Wislocki and Dempsey, 1948) to remove glycogen. Sections from formalin fixed, acetone fixed and Rossman's fluid fixed blocks were stained with haematoxylin and eosin for comparison. Sections from Zenker's fluid fixed blocks were stained with haematoxylin and phloxine.

Tissue blocks were processed in neotetrazolium to show specific succinic dehydrogenase, endogenous reductase, combined reaction and negative control (Foraker and Denham, 1953a). Frozen sections (15μ) were prepared.

Results

The general histologic pattern and histochemical cell reactions conformed to published reports (Deane, 1952; Harter, 1948; Rennels, 1951; Foraker, Denham and Johnston, 1954). Localization of sites of dehydrogenase activity in the various components of the ovary was much the same as that previously reported by Padykula (1952) and ourselves (Foraker and Denham, 1952; Foraker, Denham and Mitchell, 1953; Foraker, Denham and Johnston, 1953).

Dehydrogenase activity was manifested in the tissues incubated in neotetrazolium by deposition of black formazan granules and crystals in the cytoplasm, or in certain instances by the presence of red microdroplets in the cells (Rutenburg, Wolman and Seligman, 1953; Foraker and Denham, 1953a). In general, techniques designed to show succinic dehydrogenase and endogenous reductase showed a similar distribution of evidence of enzyme activity. The general strength of the reaction was weakest in the sections showing succinic dehydrogenase activity only, about twice as strong in the sections showing endogenous reductase activity only, and about three times as strong in the sections showing endogenous reductase activity with enhancement of the effect of succinic dehydrogenase. These latter preparations will be used for illustration, but the others revealed similar distribution qualitatively. It is not believed that these comparative strengths of reaction in the different variants of the technique represent the comparative concentrations of the enzymes overall in the tissues (Foraker and Denham, 1953a).

General comparison of the histochemical reactions of the various components of the ovary is summarized in Table I.

Primordial ova: These showed little reaction to any technique. They reacted very lightly to lipid stains. After incubation in neotetrazolium, they revealed very light red staining. These first two staining properties are related (Rutenburg *et al.*, 1953).

Reacting ova: Ova which had embarked upon the maturation process cytomorphologically also exhibited a more complex histochemical reaction pattern (Fig. 1). After incubation in neotetrazolium, they showed no evidence of formazan crystal or granule deposition but did contain many red microdroplets (Fig. 1 B). The reacting ova were the only structures in the ovaries which revealed evidence of glycogen content, and this was minimal. A faint granular reaction to the periodic acid-Schiff technique was present (Fig. 1 C), which in certain instances disappeared or was materially less in the control sections subjected to saliva digestion. The

TABLE I

Summary of Reactions of Rabbit Ovary in Pregnancy to Histochemical Techniques as Specified

Cell or Tissue Element	Dehydrogenase Activity (succinic dehydrogenase and endogenous reductase)		Lipid	Glycogen	Other Periodic Acid Positive Substances	Alkaline Phosphatase	
	Reduced Formazan	Red Staining (dissolved formazan)				Nuclear	Cytoplasmic or Other
Primordial ova ..	None	Light	Light	None	None	None	—
Reacting ova ..	None	FAIRLY STRONG	MODERATE	VERY LIGHT	VERY LIGHT	Very Light	—
Zona pellucida ..	None	MODERATE	MODERATE	None	HEAVY	—	Very Light
Follicular liquid ..	None	None	None	None	MODERATE	—	Very Light
Follicle cells ..	MODERATELY HEAVY	None	Very Light	None	None	HEAVY	MODERATE
Lutein cells ..	HEAVY	MODERATE	HEAVY	None	None	HEAVY	RATHER HEAVY
Stromal cells ..	HEAVY	Moderate	VERY HEAVY	None	None	HEAVY	Light
Hilar Vessels ..	Moderate	None	None	None	Light	MODERATE	MODERATE

reacting ova showed a moderately positive lipid stain (Fig. 2 D), and contained very light evidence of alkaline phosphatase activity (Fig. 1 D).

Zona pellucida: The zona pellucida of the reacting ova had a slightly different reaction pattern (Figs. 1 and 2). These showed light red-staining but no formazan granules as evidence of dehydrogenase activity (Fig. 1 B). They reacted moderately to lipid stains (Fig. 2 D). They showed strong reactivity to the periodic acid-Schiff technique (Figs. 1 C and 2 C), but this property was not changed by saliva digestion, hence was not due to glycogen. They showed light evidence of alkaline phosphatase activity (Fig. 1 D).

Follicular liquid: The follicular liquid showed moderate reactivity to the periodic acid-Schiff technique (unaffected by saliva digestion) second in intensity only to that seen in the zona pellucida (Fig. 2 C). Otherwise, only very light evidence of alkaline phosphatase activity was found in the follicular liquid.

Follicle cells: The follicle cells showed considerable evidence of dehydrogenase activity (Fig. 1 B). This was manifested by rather heavy cytoplasmic deposition of formazan crystals and granules with no intermingling of red microdroplets. No lipid staining of these cells was seen (Fig. 2 D) except for a very faint reaction when the follicles approached maturity. These cells manifested heavy evidence of nuclear alkaline phosphatase activity (Fig. 1 D) and a lesser cytoplasmic reaction.

Corpora lutea: The lutein cells manifested strong evidence of dehydrogenase activity (Fig. 3 B), seen as heavy cytoplasmic deposition of formazan together with considerable red microdroplet formation in the cells. The lutein cells also reacted strongly to lipid stains but not quite so strongly as stromal cells (Fig. 3 C). They showed no evidence of glycogen content. The lutein cells contained heavy nuclear and considerable cytoplasmic evidence of alkaline phosphatase activity (Fig. 3 D). Cytoplasmic

evidence of alkaline phosphatase activity was more prominent than in any other cell component of the ovary.

Stroma: The stromal cells manifested a slightly different reaction pattern. They also showed heavy evidence of dehydrogenase activity (Fig. 3 B) containing formazan granules and red microdroplets to about the same intensity as the lutein cells. Their reaction to lipid stains was stronger than that of the lutein cells (Fig. 3 C). However, they revealed very little cytoplasmic evidence of alkaline phosphatase activity (Fig. 3 D). Nuclear evidence of alkaline phosphatase activity was moderate. They showed no glycogen reaction.

Hilar vessels: These showed moderate formazan deposition manifesting dehydrogenase activity. Nuclear and cytoplasmic evidence of alkaline phosphatase activity was present. A moderate reaction to the periodic acid-Schiff technique, unaffected by saliva digestion, was found.

Discussion

The gamut of variation of histochemical reaction patterns as seen in this study offers ample material for speculation, although few definitive conclusions can be drawn.

There appears to be little to suggest a specific histochemical reaction pattern of pregnancy in the ovary. Our findings are much the same as those seen in non-gestational ovaries (Harter, 1948; Rennels, 1951; Foraker and Denham, 1952) considering the changes of stromal prominence and abundance of florid mature corpora lutea seen in the ovary in pregnancy. The principal cytomorphological difference of our material from human ovaries in pregnancy is the prominence of stromal cells. In non-gestational human ovaries, we (Foraker, Aguilar Celi and Denham, 1953) found much less stromal evidence of dehydrogenase activity than currently seen in rabbit ovaries in pregnancy, or previously reported in non-gestational rabbit ovaries (Foraker and Denham, 1952). After applying a battery of histochemical techniques, Rennels (1951) considered that his findings indicated that primary interstitial (or stromal) tissue was a source of oestrogen in rats.

Sites of hormone production in the ovary may be related to regions of dehydrogenase activity, similar to those currently reported. From their studies on rat ovaries in pregnancy, Meyer and McShan (1950) felt that the large amount of enzymes (especially succinic dehydrogenase and alkaline phosphatase) in the functional corpus luteum makes it seem reasonable that they are concerned in the growth of the corpus and in the synthesis and secretion of ketosteroids by the lutein cells. However, it is to be noted that alkaline phosphatase and dehydrogenase did not show similar distribution patterns in this study. The former was predominantly nuclear, the latter entirely cytoplasmic. In stromal cells evidence of dehydrogenase activity was strong, while there was little cytoplasmic evidence of alkaline phosphatase activity.

Perhaps the comparatively greater evidence of alkaline phosphatase activity in lutein cells correlates with Meyer and McShan's (1950) concept that the increase in alkaline phosphatase in the corpora of pregnancy and lactation is an indication that this enzyme is concerned with the synthesis and secretion of luteal hormones. Succinic dehydrogenase activity may be a better indicator of cell activity in general, be it hormone production, growth (Foraker and Denham, 1953a), exocrine secretion (Foraker and Denham, 1953b), or absorption (Foraker, Denham and Aguilar Celi, 1953) than of any specific cell function. This correlates with Padykula's summation (1952) of dehydrogenase localization as previously noted.

The patterns of glycogen and other periodic acid positive material are conventional and do not indicate any material change in pregnancy.

In tissues incubated in neotetrazolium to demonstrate sites of dehydrogenase activity, red-staining and red microdroplet reaction were seen only in structures containing fat. This is due to the fact that the reduced formazan is soluble in fat (Rutenburg *et al.*, 1953) where it appears red. However, this reaction is not a fat stain in the ordinary sense, since neotetrazolium will not react in any fashion with formalin fixed tissue.

In general, evidence of enzyme activity occurred in presumed sites of hormone production in this study. Marked evidence of alkaline phosphatase and dehydrogenase activity was found in the corpora lutea, the site of pro-

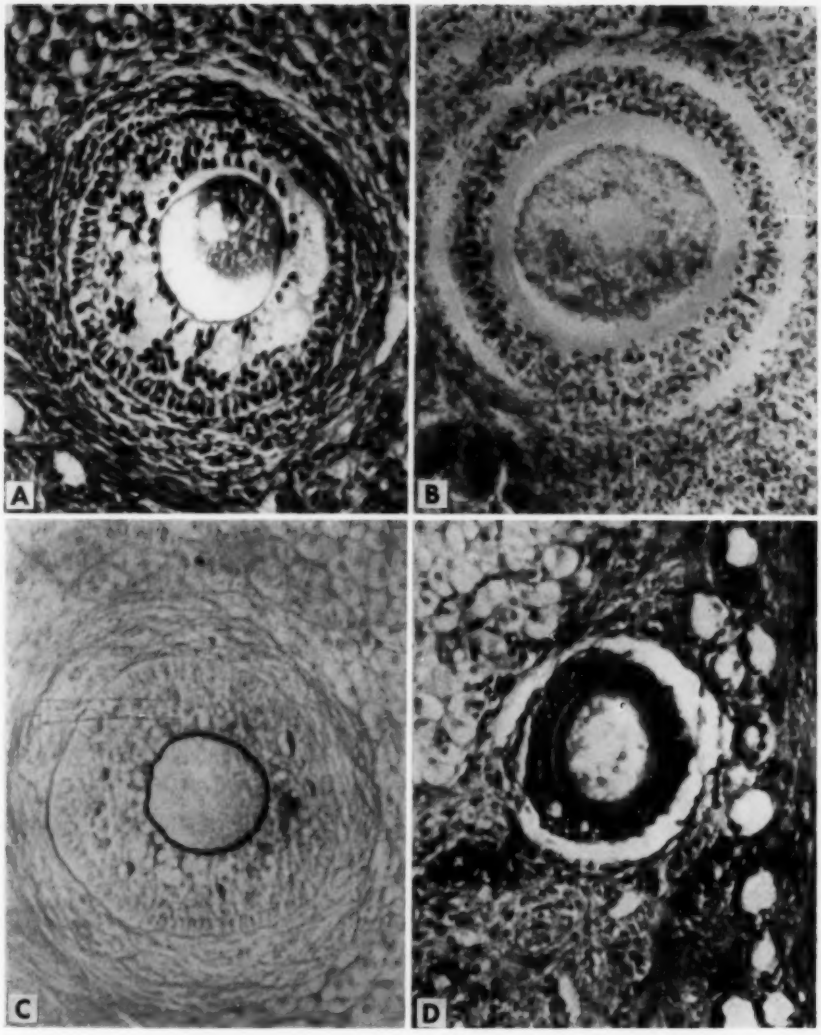

FIG. 1

A.—Haematoxylin and eosin. Ova with adjacent structures. ×270. B.—Section from same ovary incubated in neotetrazolium to demonstrate sites of dehydrogenase activity. Red microdroplet staining only of ovum. Very light red staining of zona pellucida. Considerable formazan granule deposition in follicle cells as evidence of dehydrogenase activity. ×270. C.—Periodic acid technique. Light reaction in ovum. This is diminished by previous saliva digestion, hence is partly due to glycogen. Heavy reaction of zona pellucida is not due to glycogen. ×270. D.—Alkaline phosphatase. Light reaction in ovum. Zona pellucida shows moderate reaction. Follicle cells are rather strongly reactive. ×270.

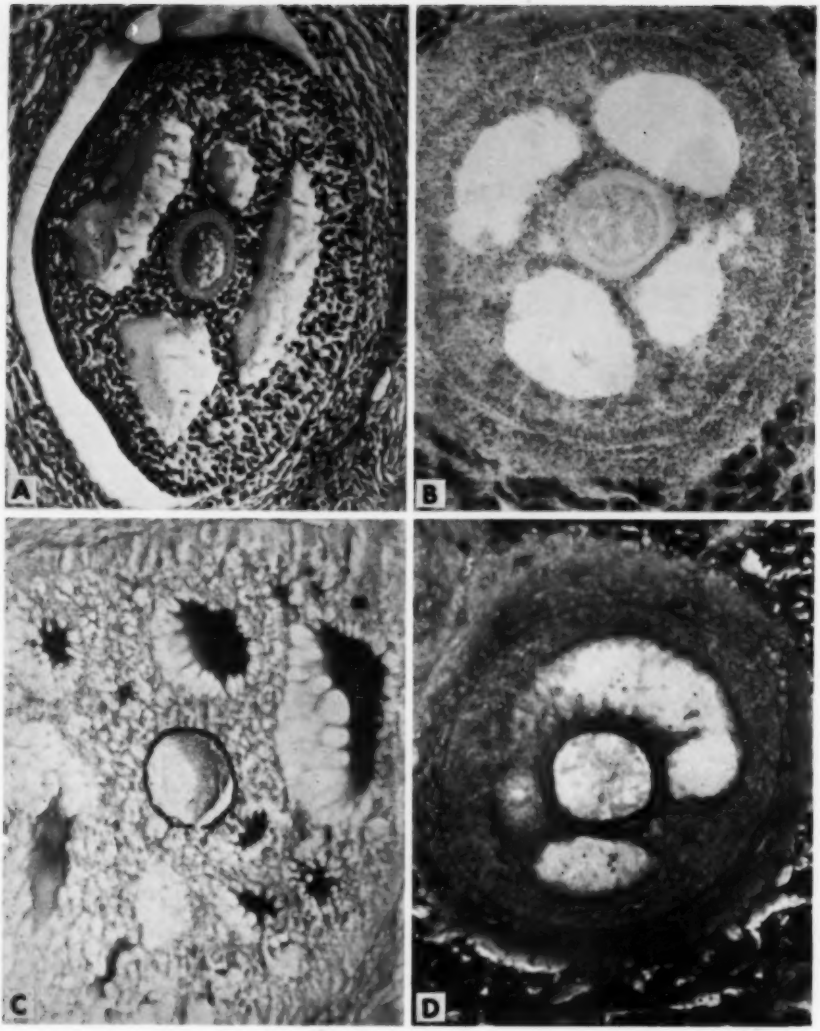

FIG. 2

A.—Haematoxylin and eosin. Developing follicle. ×135. B.—Neotetrazolium section. Distribution of evidences of dehydrogenase activity in ovum and follicle cells unchanged. Adjacent stromal cells contain heavy formazan deposition. ×135. C.—Periodic acid technique. Essentially the same reaction pattern as Fig. 1 C. However, the follicular liquid has a fairly strong reaction, not due to glycogen. ×135. D.—Sudan black B (lipid). Very light staining of ovum. Zona pellucida reacts moderately. Very little reaction in follicle cells. ×135.

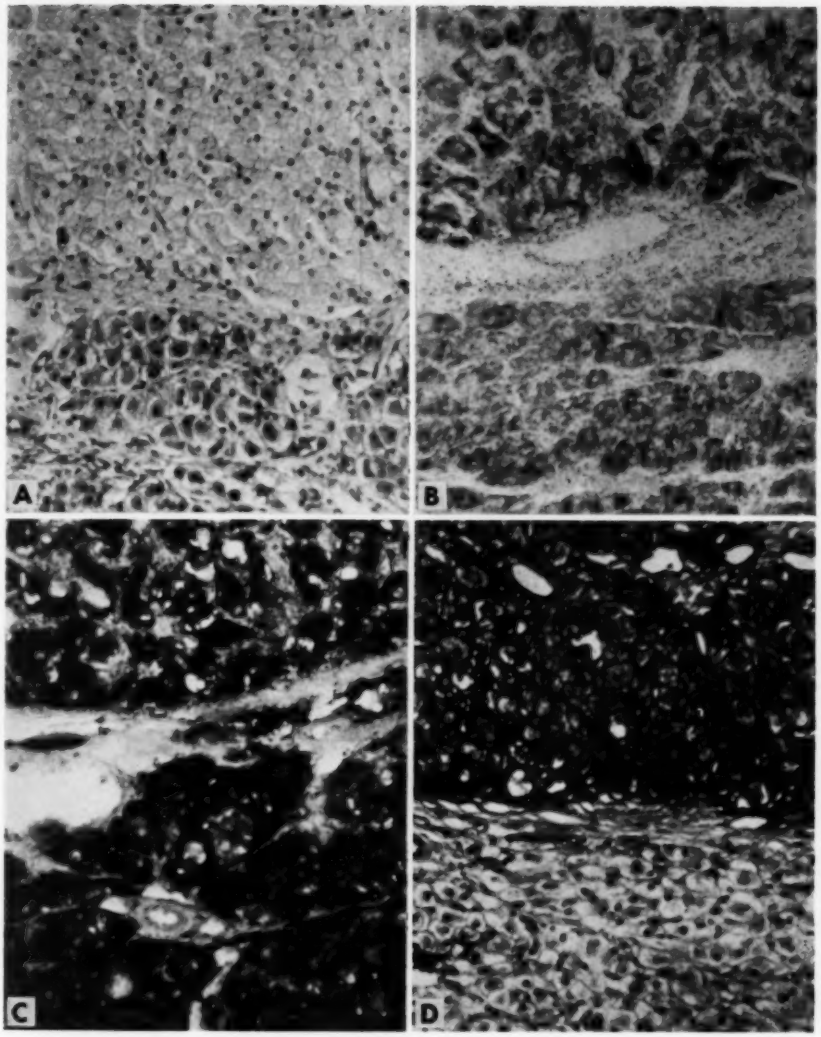

FIG. 3

A.—Haematoxylin and eosin section. Lutein cells in mature corpus luteum above, and stromal cells below. ×165. B.—Neotetrazolium section. Heavy cytoplasmic evidence of dehydrogenase activity in both lutein and stromal cells. ×165. C.—Sudan black. Heavy lipid staining in both lutein and stromal cells. ×165. D.—Alkaline phosphatase. Heavy evidence of alkaline phosphatase activity in nuclei of lutein and stromal cells. However, lutein cells exhibit much stronger cytoplasmic staining than do stromal cells. ×165.

A.G.F., S.W.D., D.D.M.

duction of luteal hormone. The stromal cells, presumed sites of oestrogen production, showed marked evidence of dehydrogenase activity, but less evidence of alkaline phosphatase activity.

Summary

Sites of dehydrogenase and alkaline phosphatase activity, lipid and glycogen were studied in mid-gestational rabbit ovaries. The results showed:

(1) Marked evidence of dehydrogenase and alkaline phosphatase activity and lipid in lutein cells.

(2) Marked evidence of dehydrogenase activity and lipid, and less evidence of alkaline phosphatase activity in stromal cells.

(3) Lesser degrees of evidence of enzyme activity in certain other cell components.

(4) Glycogen and other periodic acid-Schiff positive substances, and lipid in conventionally described distribution patterns.

Possible correlation of sites of enzyme activity with sites of hormone production was reviewed.

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RUPTURE OF THE UTERUS DURING PREGNANCY FOLLOWING PREVIOUS INVERSION

BY

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SPONTANEOUS rupture of the uterus during pregnancy is a rare phenomenon. Scar formation in the uterine wall, due to a wide variety of causes, is the usual predisposing factor. Rupture of Caesarean section scars, particularly the classical type, constitutes the majority of recorded cases. Most textbooks, including those of DeLee and Greenhill (1951), Munro Kerr and Chassar Moir (1949), and Beck (1951), give comprehensive lists of other types of trauma, including manual removal of the placenta, which have been noted as preceding rupture of the uterus during pregnancy. They do not, however, record manual reposition of the acutely inverted uterus and a search of the literature has failed to reveal any other record of the following sequence of events.

CASE REPORT

Mrs. A. was aged 24 years, 2-gravida.

Her last period was on 9th November, 1952, giving her an estimated date of confinement of 16th August, 1953. The pregnancy was uneventful until the morning of 26th July. On waking up she turned over suddenly in bed and immediately experienced severe pain in the upper abdomen and became profoundly collapsed.

Examination revealed a shocked patient. The uterus was a little small for her dates and was tender. It was possible to define the lie of the foetus and to feel a vertex engaged in the pelvic brim. Vaginal examination confirmed the vertex presentation. The cervix admitted one finger. No vaginal loss was present, no uterine contractions were felt, and the patient was not in labour. After transfusion the patient was transferred to the Bowthorpe Maternity Hospital.

The patient's past history of her first confinement was as follows. She was seen as an emergency shortly after delivery on 9th January, 1951. After completion of the third stage a massive post-partum haemorrhage had taken place. Examination revealed a pulseless patient with no registerable blood pressure. A vaginal examination disclosed that acute inversion of the uterus was present. After rapid transfusion the uterus was replaced without difficulty under general anaesthesia. In all, 6 pints of blood were given. The puerperium was uneventful.

On the present occasion intra-peritoneal haemorrhage was diagnosed and the possibility of rupture of the uterus considered. After further transfusion the abdomen was opened by a mid-line incision. A large quantity of blood clot and fluid blood was present in the peritoneal cavity. At the fundus of the uterus on its posterior aspect was an irregular tear about 4 inches long. Through this was protruding an area of placenta the size of a 5-shilling piece.

The baby, which was dead, was removed from the uterus by a vertical incision extending down the anterior wall of the uterus from the laceration. A rapid sub-total hysterectomy was performed and the abdomen cleared of clots. At the end of the operation the patient's condition was satisfactory. In all, 11 pints of blood were transfused.

The post-operative period passed without anxiety and the patient was discharged home on the thirteenth day.

Trauma and subsequent scar formation associated with manual reposition of the uterus must be deemed the factor which had produced a weak area in the fundus of the uterus in this case. That some local inflammatory reaction had been present was shown by the presence of omental adhesions at the point of rupture.

Herbut (1953) and Couvelaire (1906) draw attention to the effect of the situation of the placenta in relation to uterine scarring. They consider that rupture is more likely when placental implantation covers the scarred area. The present case supports this view.

The records relating to inversion of the uterus have been examined. Das (1940) and Miller (1927) have followed up the subsequent history of these cases. In 350 patients they found no instance of rupture of the uterus in pregnancy.

DeLee and Greenhill state that "when the inversion was corrected by operation uncomplicated delivery may be anticipated and

rupture of the uterus need not be feared". The implication is that some similar case to the present one had occurred within this writer's knowledge.

Summary

A case of rupture of the uterus occurring spontaneously in the thirty-seventh week of pregnancy is recorded. Inversion of the uterus had been treated by manual reposition after delivery of the patient's first child 2 years earlier. Trauma, associated with the replacement of the uterus, is considered to be the origin of the scarring which predisposed to rupture.

I should like to acknowledge the great help rendered by Dr. C. Cameron of the East Anglian Blood Transfusion Service in this case.

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RUPTURE OF THE UTERUS

A report of Fifty Cases which occurred in Two and a Half Years at Baragwanath Hospital, Johannesburg, South Africa

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RUPTURE of the uterus is of particular interest to obstetricians in South Africa, who practise among the Bantu people, as this accident of pregnancy is probably more prone to occur among the coloured races of this Continent than elsewhere in the world.

Heyns (1946) states that the South African Bantu woman is a superior parturient, in that she is able to deliver a child which weighs only slightly less than that of the European through a pelvis which is most definitely smaller. However, this very characteristic of the Bantu is at times a factor in the production of rupture of the uterus.

INCIDENCE

The incidence of rupture varies considerably in the reports of various authors found in the literature. The highest incidence is apparently that of the present series—50 cases of rupture in 6,857 deliveries—1 in 137. Whitacre and Fang (1942) of Peiping report an incidence of 1 rupture in 200 deliveries; Evans (1953) of the Bridgman Memorial Maternity Hospital for Non-Europeans describes an incidence of 8 ruptures in 2,789 deliveries—(1 in 349), while Naylor (1948) who analyzed the figures of the same hospital, but in an earlier series, found that there was 1 rupture in every 525 deliveries.

The lowest incidence found in a study of the literature is that of Dugger (1945) who collected 105 cases of rupture which occurred in 318,103 deliveries—1 in 3,029. The incidences quoted by other American writers are as follows:

Author	Years	No. of Deliveries	No. of Ruptures	Incidence
Sheldon (1936) ..	1918–1934	47,554	26	1 in 1825
Lynch (1945) ..	1920–1945	41,706	44	1 ,, 1,118
Morrison and Douglas (1945)	1920–1943	65,916	45	1 ,, 1,463
Delfs and Eastman (1945) ..	1920–1945	53,574	53	1 ,, 1,010
Acken (1940) ..	1924–1939	25,935	15	1 ,, 1,725
Bill, Barney and Melody (1944)	1925–1941	69,391	23	1 ,, 2,756
Dugger (1945) ..	1931–1941	318,103	105	1 ,, 3,029
Brieton (1950) ..	1932–1946	117,753	57	1 ,, 1,961

In England Simons (1950) describes 15 cases which occurred in 33,492 deliveries (1 in 2,233). It is apparent that the incidence of this accident is greater in coloured races.

AGE

In the cases of ruptured uterus in this series, the age of the patient varied between 15 and 45 years—with an average age of 30·5 years. Eight patients were in the age group 15 to 24 years, 20 were between 25 and 30 years, 19 were between 31 and 35 years, and 10 were between 36 and 40 years. Three patients were aged 43, 44 and 45 respectively.

The largest group fell in the age group 25 to 30 years. Of the patients who died as a result of the rupture of the uterus the youngest was aged 23 years and the oldest 45 years, the average age being 32·6 years. However, the average age of those patients who recovered was 30 years.

Posner, Smith and Trambert (1951) found in their analysis that the younger patient survived the accident.

In the 50 cases of rupture, the range of parity was between primigravida and gravida-13, the average being 4·2. There were 4 patients who were primigravida and these were aged 15, 23, 28 and 45 years and 3 patients died as a result of the accident.

There were 46 multigravidae of whom 31 had been pregnant between 1 and 4 times and 15 had been pregnant between 5 and 13 times.

Contrary to the generally accepted concept of the grand multipara being more liable to this accident the greater number of patients had been pregnant 4 times and under. In the Posner series (1951) the average parity was 4·1, while Delfs and Eastman (1945) found that, in 17 cases in their series, the parity averaged 6·4. Bill, Barney and Melody (1944) quote the ratio 6·6 multiparae to 1 primipara. Schumann (1936) states that the accident is more liable to occur in the multipara in the ratio of 12 to 1, DeLee and Greenhill (1943) quote the ratio of 8 to 1, and the present series reveals a ratio of 11·5 to 1.

All authors agree that multiparity is one of the chief factors in the cause of rupture of the uterus (Munro Kerr, 1933; Solomons, 1934; Mahfouz 1932; Green-Armytage, 1936; White, 1942).

The Extent of Rupture

Rupture of the uterus may be complete or incomplete. The complete type occurs through all layers of the uterus and communicates with the general peritoneal cavity, while incomplete rupture involves the muscle coat only, the peritoneal covering of the uterus remains intact. Complete rupture is more common in this series, 38 patients (76 per cent) were of this type and 12 patients (24 per cent) had partial or incomplete ruptures. This is in keeping with the published results of Morrison and Douglas (1945)—80 per cent complete; Bill, Barney and Melody (1944)—76·9 per cent; and Naylor (1948)—76·9 per cent.

The Site of Rupture

The lower uterine segment of the uterus was involved in the majority of cases in this series, particularly in the primary spontaneous type of rupture. In the traumatic type of rupture it was found that a combination of sites was usual, the tear extending from the lower uterine segment into the upper segment.

Anterior Surface of Lower Segment

Transverse rupture	26 cases
Vertical rupture	9 cases

Posterior Surface of Lower Segment

Transverse rupture	1 case
Vertical rupture	8 cases

Other Sites

Vertical rupture on lateral surfaces of the lower uterine segment	7 cases
Combination of sites	7 cases
Upper segment of uterus	2 cases

Old Caesarean Section Scars

Lower segment	3 cases
Upper segment	2 cases
Traumatic rupture, lower segment	1 case

The incidence of rupture occurring at the site of a previous Caesarean section is 10 per cent and the fact that the lower segment has been involved more often than the upper segment is probably due to the greater use of the former type of Caesarean section operation. Lawrence (1949), in his review on the danger of rupture through an old lower segment Caesarean section scar, concludes that the incidence of rupture is sufficiently small to justify a trial of labour in a successive pregnancy and labour. He says that for all practical purposes the danger of rupture is non-existent!

Brieton (1950) who analyzed the figures from 5 hospitals found that 2·8 per cent of 246 pregnancies following Caesarean section had ended in rupture. His series included 4 classical and 3 lower segment incisions. In the spontaneous type of rupture (21 cases)—10 were in lower segment—6 included both upper and lower segment and 5 involved the corpus alone.

Aetiology of Rupture

Many and various are the theories postulated for the causation of this accident. However, most

writers agree that not infrequently the cause escapes logical explanation. Powers and Gerard (1944), Delfs and Eastman (1945), Goldstein (1947), and Murray (1902) all state that in some instances, the cause cannot be explained satisfactorily. In the present series there are at least 5 cases in which it is not possible to account for the rupture. In 4 cases the probable cause was multiparity (Para. 10, 8, 7 and 5) while in the remaining case, a primipara, labour had been in progress 8½ hours with no disproportion, no contracted pelvis and no history of previous trauma to the uterus, when it ruptured spontaneously through all layers.

Rupture may be spontaneous or traumatic. Spontaneous types may occur in an undamaged uterus (primary) or in a uterus previously incised (secondary) as, for example, previous Caesarean section scars, myomectomy-incisions, cornual resections for ectopic pregnancy, or possibly where curettage may have damaged the uterine muscle. In the secondary types of rupture the explanation is not hard to find, but, as the incidence of this type is not high, attention is turned to the primary spontaneous type of rupture in an undamaged uterus.

In patients in whom labour has lasted more than 24 hours, with satisfactory uterine action, the uterus may rupture quite spontaneously in the presence of obstruction to the passage of the foetus through the birth canal. Of great importance is the type and duration of the uterine contraction in those cases in which activity of the uterus becomes more and more severe, with little or no progress and non-engagement of the presenting part. It is known that the multiparous uterus reacts to obstruction to delivery of the foetus by acting more strongly and that minor degrees of disproportion become major as the number of pregnancies increases.

Watt (1950) does stress the importance of the fact that multiparity of itself does not necessarily mean an easy labour and this is borne out in the present series.

Traumatic rupture of the uterus usually follows faulty judgment in cases of obstructed labour and failure to recognize that the uterus has been dangerously thinned out and overstretched. In this type of case, to persist with attempts at vaginal delivery by means of decapitation, internal version and breech extraction or craniotomy usually ends in disaster.

Other causes of traumatic rupture such as direct blows on the uterus and falls on the abdomen have not occurred in this series. Instances of rupture due to perforation of the lower uterine segment by means of an instrument such as the obstetric forceps or perforator do not occur frequently.

In this series, spontaneous rupture occurred in 34 or 68 per cent of the patients, while traumatic rupture occurred in 16 or 32 per cent. Primary rupture occurred in 45 or 90 per cent and 5 cases, 10 per cent, had a secondary spontaneous rupture through previous Caesarean section scars. Seventeen patients were admitted to the unit with the uterus already ruptured, while the balance actually ruptured in the ward.

The aetiology of rupture in the present series does follow the oft-described pattern, with the possible exception of one predisposing factor. The South African Bantu parturient is very prone to begin voluntary bearing down efforts long before the cervix is fully taken up and dilated. This tends to cause oedema of the cervix and offers mechanical obstruction to the birth of the foetus. In 13 patients this single factor was considered to be the sole cause of the rupture, in the absence of disproportion, contracted pelvis or malpresentation. Particularly is this complication to be feared in the multipara with a malpresentation of the foetus. This excessive and prolonged bearing down results in excessive thinning out of the lower segment and the formation of the Bandl retraction ring, and rupture has been seen to occur while the patient was being examined.

Obstructed labour was the chief factor in 42 of the 50 cases while in 29 patients cephalopelvic disproportion predisposed to the rupture. Malpresentation of the foetus was present in 6 cases (4 transverse and 2 brow presentations) and in 3 patients only multiparity could be blamed for the accident. In 1 case, a primipara, no cause could be found.

Rupture of the uterus ascribed to other causes such as congenital abnormalities of the uterus, general systemic disease, fibroid uterus and neoplasms were not encountered in the patients comprising this series. Munro Kerr and Chassar

Moir (1949) state that an increase of fibrous tissue occurs in uterine muscle subsequent to each pregnancy and thus, after multiple pregnancies, the likelihood of rupture is increased. Potter (1930) found microscopic evidence of muscle fibre pathology in cases of rupture of the uterus in 50 per cent of his material and DeLee (1947) states that rupture was due to the weakness of muscle fibres, scars, inflammations and residues of previous labours. Murphy (1947) considers the primary causative factor to be the stronger acting uterus of the multiparous patient. Jeffcoate (1950) agrees with this statement and is of the opinion that the primiparous uterus reacts to obstruction by hypotonic action. F. J. Browne (1951) states that it has been found that in the older and greater parous women, the tendency to rupture is much increased.

An interesting cause for rupture is that offered by Siegler (1933) and De Sa (1934), who stated that, in cases of placenta praevia, excessive invasion of the lower segment weakens the uterus and thus predisposes to rupture. This theory has not found support in the literature on the subject. Three cases of placenta praevia accreta in the lower segment are known to the author—without any rupture occurring.

In the cases in whom a traumatic rupture of the uterus occurred, analysis shows that in only 1 case was the rupture caused by direct trauma to the uterus. This occurred in a patient on whom a craniotomy was to be done; the perforator slipped and perforated the lower segment. In the balance of cases the rupture was caused by indirect trauma, viz., decapitation—3 cases, internal version after failed forceps—4 cases, internal version for transverse lie—2 cases, craniotomy—6 cases, failed forceps—1 case and internal version on second twin—1 case.

Of the 16 cases of rupture who died, there were 7 traumatic ruptures (43·7 per cent). Gordon and Rosenthal (1949) analyzed 60 maternal deaths due to rupture and found that 37·2 per cent were due to trauma. Morrison and Douglas (1945) collected 45 cases and found a 40 per cent incidence of trauma, and Brieton (1950) quotes an incidence of 17·6 per cent.

This high incidence of rupture caused by intra-uterine manipulations has led to a reconsideration of the predisposing causes of this type of rupture. It has postulated that in those cases, in which the uterus has been overacting in the presence of obstruction, whether due to disproportion or malpresentation, and a Bandl retraction ring has developed, it is by far safer for the mother to deliver the child by the abdominal route, even if the foetus is no longer alive, rather than to attempt delivery *per vias naturales*.

The duration of labour in this series varied considerably, the shortest time being 3¾ hours and the longest 144 hours—with an average duration of 24·8 hours.

Diagnosis

The diagnosis of the condition did not offer any great difficulties, since the majority of cases presented classical symptoms.

In 24 cases in whom rupture occurred before delivery of the foetus, a history was obtained of sharp sudden tearing pain, with cessation of rhythmic labour pains and a feeling of relief. A constant feature in these patients was the onset of vaginal bleeding, which at times was brisk and profuse.

The foetus was felt "under the skin" and dullness to percussion in the flanks was found in all these cases where rupture was complete.

In 16 cases the rupture was discovered during routine manual exploration of the uterus after delivery of the foetus by difficult intra-uterine manipulations. It is routine procedure in this unit to explore the uterus after such manipulations as internal version, craniotomy, difficult forceps delivery and breech extractions, because these are the manœuvres which have been found to be associated with rupture.

In 10 patients rupture was suspected to be imminent or to have occurred very recently—and at laparotomy for Caesarean section this was found to have occurred.

In 2 instances the damage was unsuspected and the patients died suddenly. At autopsy examination, what had been thought to be local damage to the vagina was found to be extensive rupture of the uterus involving the base of the broad ligament.

In this series, a sign which was found to be constant in all cases, except ruptures through previous scars, was the presence of blood stained

urine. The amount of blood varied from a moderate red staining of urine to the presence of frank red or dark altered blood. Great stress is placed on this one sign, in those cases where predisposition to rupture is present, because it is interpreted as signifying danger of rupture. In all cases who were subjected to laparotomy, the bladder was found to be very oedematous, with haemorrhagic areas under the serosal coat, and the organ was always found to be occupying a high position in the abdomen.

Treatment

In the 50 cases of ruptured uterus, repair of the uterus was carried out in 28 instances. The uterus was removed by subtotal hysterectomy in 11 cases, and 11 patients were not subjected to operation—for varying reasons. Thus of those cases who were subjected to surgery (39) repair was considered to offer the best chance to the patient in 28 instances (71·8 per cent).

Routine anti-shock therapy, blood transfusions under pressure, A.C.T.H. drip therapy and subsequent laparotomy was the method of choice used in this hospital in most cases.

The number of repaired uteri is higher in this series than in published figures. The probable reasons for this are, firstly, that the South African Bantu woman often refuses operation, even when death is the alternative, if she is not assured that her uterus will be conserved. The reasoning behind this is probably unique—and briefly, is based on the fact that the male Bantu purchases his wife—and offspring seal the bargain. If a woman does not have any chance of producing children (menstruation being counted as a sign of possible fertility) she is discarded by the husband and the latter may then claim his purchase price. This, of course, led to attempts at repair, which probably would not have been tried under ordinary circumstances, and a fair degree of skill resulted.

Secondly, it was found that repair was actually less shocking to the mother than hysterectomy. In those patients who have had 4 or more infants precautionary sterilization was also practised, particularly when the uterus was considered to be too extensively damaged to risk subjecting it to further pregnancies.

Mortality

There were 16 deaths in this group—a mortality rate of 32·0 per cent. The rupture was complete in 15 cases and incomplete in one case; this latter patient died as a result of gas gangrene infection. Three of the 15 patients died undelivered because they failed to respond to anti-shock therapy and therefore could not be subjected to surgery.

Five patients had the uterus repaired but died, and subtotal hysterectomy was performed in 2 instances to improve the patients' condition, and 1 rupture was not diagnosed.

The time of death varied considerably as follows:

Soon after admission (up to 5 hours) (3 died undelivered)	6 cases
Died first to third post-operative day	6 cases
Died on twelfth post-operative day	2 cases
Died during operation	2 cases
	16 cases

Cause of Death

By far the commonest cause of death was shock and haemorrhage (11 cases), peritonitis was found in 3 patients, 1 died of pulmonary embolism on the 12th post-operative day and 1 died of gas gangrene infection.

A constant feature in 9 cases (3 who died undelivered and 6 on whom no operation was possible) was extensive destruction and tearing of the peritoneum of the broad ligament. In all these cases it was never possible to overcome the profound shocked state, and it appears as though the damage in this area caused shock of such a degree, that routine anti-shock therapy failed to halt the process.

In all cases of complete rupture of the uterus in this series a constant feature was the large quantity of blood found in the peritoneal cavity —and estimated to vary between 2 and 3 litres.

Results

Maternal Deaths—16 (15 complete and 1 incomplete).

5 ruptures were repaired.

2 hysterectomies were performed.

9 patients were not subjected to operation.

Patients who survived—34.

23 were of the complete type (15 repaired—8 hysterectomy).

11 were of the incomplete type (7 repaired—1 hysterectomy).

3 no operation.

Complete Ruptures—Total 38.

20 repaired.

10 hysterectomy.

8 no operation (nil survivals).

Total Series—50.

28 repaired (5 deaths).

11 hysterectomy (2 deaths).

11 no operation (9 deaths).

In the 2½ years in which these ruptured uteri occurred there were 53 maternal deaths (0·5 per cent). Rupture of the uterus constituted 16 or 30·1 per cent of these deaths.

Summary and Conclusions

There is a high incidence of rupture of the uterus in the Bantu of Johannesburg—1 rupture for every 137 deliveries.

Rupture occurs more frequently in multiparae (11½ multiparae to 1 primipara).

Rupture is more often complete than partial or incomplete. The incidence of complete rupture was 76·0 per cent.

The site of rupture was more often the anterior lower segment and was transverse in direction. The aetiology of rupture (spontaneous type) includes obstructed labour, malpresentations, disproportion and, in the South African Bantu female, premature bearing-down on an incompletely dilated cervix.

In the diagnosis of rupture the characteristic sudden sharp pain, with cessation of labour pains occurred in 41 per cent of cases. The foetus could be palpated "under the skin" in most cases and a constant feature in primary spontaneous ruptures was the presence of blood in the urine.

Treatment consisted of repair of the uterus in 28 of 50 cases, hysterectomy in 11 patients and in 11 cases no operation was possible. Anti-shock measures, blood transfusion under pressure, A.C.T.H. by intravenous drip therapy all formed adjuncts to surgery.

A mortality of 32·0 per cent occurred in the series. In the maternal deaths all but 1 rupture was complete, and 3 patients died undelivered.

The commonest causes of death were shock and haemorrhage (11 cases), peritonitis was next (3 cases), 1 was from pulmonary embolism and 1 from gas gangrene. Six patients died within 5 hours of admission and 10 died between the first and twenty-second post-operative day.

I wish to thank Dr. J. D. Allen, Medical Superintendent of Baragwanath Hospital, for permission to use the case histories.

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GENETIC HAZARDS IN OVARIAN RADIATION

BY

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INFORMED clinical radiologists are extremely cautious in the use of diagnostic and therapeutic radiations or of extensive fluoroscopy in the pelvic region of women in the reproductive age range. In spite of this caution among radiologists there is a small group of obstetricians and gynaecologists who are using X-rays, beamed directly to the ovary, in an attempt to overcome sterility. The most recent report of such procedures is that of Kaplan (1953). A substantial part of this paper is given over to quotations from other papers by Rubin (1952), Israel (1952) and Wolf (1950), all of whom seem to agree with Kaplan. The main thesis of this paper, if allowed to go unchallenged, would give the erroneous impression that X-irradiation is used extensively in the United States to overcome sterility. Dr. Kaplan has reported that ovarian X-irradiation of selected cases has resulted in some 35 per cent success, and claims several generations of progeny free from teratologies. There are no controls for such data, such as X-irradiation of the pituitary gland alone or a phantom radiation. It is true that there are some reports of success by the various authors mentioned above. While this would be encouraging news to sterile couples, who comprise approximately 20 per cent of all married couples, it is the urgent duty of those trained in genetics, embryology, and radiobiology to point out the possible hazards that do exist in such a procedure. It is invariably those gynaecologists and obstetricians who have never had direct experience in experimental genetics or embryology who are willing to prescribe X-rays in order to help a woman to have a baby. Fortunately those doctors are relatively few in number. More and more medical schools are recognizing the importance of exposing their students to at least a basic knowledge of the mechanisms of heredity.

In his discussion Dr. Kaplan confuses the egg and the embryo, the ovary and the foetus, *Drosophila* and human heredity, X-irradiation of the gonad and whole body X-irradiation. And, of course, his data can be challenged because there are no controls. One could present evidence from animal experimentation to contradict almost every assertion in this paper. And there is every reason to believe similar mechanisms of heredity apply to the human. It will suffice, however, to take one of his major contentions and discuss it alone in order to illustrate the harm that inadequate information may do. Reference is made to the idea of recovery from X-irradiation injury.

Dr. Kaplan quotes from Rubin (1953) as follows: "There is another basic biologic difference between irradiating *Drosophila* eggs and the ovaries of non-pregnant women, namely, in the reproductive cycles. The *Drosophila* reproduces itself in about 10 days, some 30 generations being produced in one year, although its life cycle is about 90 days. After irradiation, little time is left between generations for full *recovery** from its effect to take place." Kaplan himself says: "These successful results give evidence that whatever damage may have been done to the reproductive organs of these sterile women was *temporary** and had left *no permanent effect** on the genes of their subsequent second and third generation progeny." Thus, both Rubin and Kaplan seem to admit the probability of X-irradiation damage and they postulate "recovery" from whatever radiation damage there might be. On the basis

* The present author's *italics*.

of the recovery factor they recommend X-irradiation of the ovaries. The idea of recovery probably stems from experience in subsiding visible erythema, following X-rays. However, the genetic damage to the ovaries or testes is quite different in that it is never visible and, in contrast with somatic cells, is evident only through reproduction.

Now, what are the facts from radiobiological experimentation?

1. *Recovery from X-irradiations of the Gonads:* Recovery, in the sense of the return of a chromosome* to its original state following X-ray alteration, is unknown. If an altered or damaged chromosome can survive, divide, and segregate to daughter cells, each cell will bear the altered chromosome no matter whether it is a somatic or a reproductive cell. At levels of X-irradiation far below that which will produce detectable chromosome changes, there is experimental evidence to show that mutations may be brought about by *less than a single roentgen of X-irradiation*. Muller (1954), the Nobel Prize geneticist, states, in regard to X-irradiation of the gonads, that there is "no dose so small as to give no mutations at all; each individual ionization, and probably each activation of an atom, carries its definite chance of producing a mutation". There is no other external factor even remotely as effective as X-rays in the induction of mutational changes in the genes. And there is no known return (i.e., recovery) of these genic mutations to their original state. Such mutated genes will be passed along from generation to generation as long as there are progeny and in a manner identical with the non-mutated genes. In other words, X-radiation changes at the gene or chromosome level are irrevocable (i.e., irreparable). While such changes are invisible they are nonetheless real, eventually appearing in some way to affect progeny. The fact that man, with 24 pairs of chromosomes, has probably upwards of 40,000 genes in each germ cell suggests that his gametes may prove to be better targets than those of *Drosophila* when exposed to ionizing radiations. There is no recovery from any radiation-induced genic change. And Muller (1954) writes: "On the average, each newly mutated gene, no matter how small the detriment it occasions, eventually takes its toll in the form of making a major contribution to the extinction of the line of descent."

2. *Cumulative Effect of Radiations:* The gonad is a reserve of primitive and maturing germ cells, every one of which is subjected to genic and/or chromosomal changes in the event that either the gonad alone or the body as a whole is exposed to penetrating X-rays. Radiations are non-selective and can alter any cell of the body, but only changes in the reproductive cells will affect the progeny. X-rays can cause cancer in the ovary or a mutation in an ovum. A dose of 1 roentgen per hour for 300 hours will have the same effect on the germ cells exposed (and hence on heredity) as would a single dose of 300 r in 1 minute. Radiation damage to the germ cells is cumulative without regard for time. Thus, when one compares *Drosophila* experiments with human heredity the facts point toward the adverse situation for man, who has a much longer period of reproductive life during which radiation damage to the reproductive cells could be accumulated. The frequency of gene mutations in any living organism is exactly proportional to the total dose of radiation reaching the germ cells. Not only is there no recovery, but X-irradiation changes are cumulative in the germ cells exposed.

3. *Effect of Radiations upon Heredity:* No geneticist would predict that monstrosities would appear in the first generation following X-irradiation of the gonads. He would predict, however, that for a dose of 80 roentgens of exposure of the gonad there could be expected a doubling of the normal rate of mutations; that the majority of mutations would be deleterious; and that such radiation-induced mutational changes are hereditary and will persist as long as there are descendents of the exposed individuals. A mutation need not be a monstrosity, but it stands a 90 per cent chance of adding to the load of inherited human ills.

High level exposure will bring on sterility. The fact that in the male sterility does not begin for a few weeks, lasts several months, and then

* In this discussion of hazards, our major concern is the hereditary material, i.e., the chromosome and the gene.

may disappear in favour of fertility, does not alter in any sense our basic knowledge of the hereditary mechanism. This is often called temporary sterility and is brought about by the fact that the gonad contains germ cells in different stages of maturation and of differing radiosensitivities. The fully matured spermatozoa are not as easily killed by X-rays as are the spermatocytes from which they develop, so that sterility is never immediate. Likewise, the early primordial germ cells are even less radiosensitive. When they have reached the spermatozoon stage, they cause the individual apparently to "recover" fertility. These cells, exposed to the same X-rays but at an earlier stage of maturation, are nonetheless altered by the X-rays so far as their hereditary influence is concerned. A gonad once sterilized by X-rays, later to produce viable germ cells, will, without the slightest doubt, carry germ cells bearing nearly the maximum number of mutated genes. Thus, there is no recovery from any X-irradiation-induced mutation, and the effects are cumulative and permanent.

The difficulty in this area of discussion arises out of the fact that human history has been short, human litters are small and the breeding is slow so that there has not been adequate time to assemble as much data as we have from faster breeding animals. Nevertheless, there is every reason to believe that the mechanisms of animal heredity apply to the human. There are known already over 60 dominant human mutations which follow the Mendelian Laws of Heredity, from absence of patella, through glaucoma, to trophoedema and many recessive mutations from albinism to von Gierke's disease. It seems difficult for some people to realize that the same laws of heredity, discovered through painstaking studies with the fast breeding and prolific fruit fly, *Drosophila*, apply in exactly the same manner to all animals studied, including man.

The essential conflict is very simple. It exists between the genetically untrained obstetrician who will do anything he can to help his patient have a child, regardless of any eventualities, and the experimentally trained radiobiologist who will avoid even the remotest possibility of interfering with a hereditary line, whether there is a chance of a deleterious mutation appearing in 1955 or a thousand years hence.

The professional geneticist is as ill-qualified to diagnose an X-ray film as is the obstetrician or radiotherapist to predict the hereditary possibilities attendant upon gonad X-irradiation for the purpose of overcoming sterility. While no geneticist would predict an influx of monstrosities with the increasing use of nuclear energy in medicine, research, and in industry, every geneticist would suggest that the clinical radiologist apprise his patient with the fact that the X-irradiation of her ovaries for the purpose of overcoming sterility will alter permanently the hereditary line with which she has been entrusted. If she is willing to accept the responsibility of passing along to her posterity a genetically weakened set of genes the choice will then be hers, not that of her doctor. There is still the possibility that history will call her to account, along with others similarly treated by such as Kaplan.

Medicine, research, and industry have never had such a marvellous tool as nuclear energy for the advancement of civilization as a whole. It is the simple purpose of this article to point out that this same tool, if it is used to tamper with the hereditary mechanism through direct exposure of the gonads, may well alter the quality and survival value of civilization.

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THE EXPERIMENTAL PRODUCTION OF LIPOID IN THE UTERUS OF THE GUINEA-PIG

BY

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NICOL and Snell (1954) showed in the guinea-pig that during the oestrous cycle lipoid is present in the lining epithelium of the uterine horns and distal part of the uterine body and is most intense during the period of activity of the corpus luteum. They also showed that lipoid is practically absent from the epithelium of the uterine horns about the time of implantation and that in the stratum compactum of the endometrium a small number of large lipoid-containing cells is present throughout the cycle, being greatest in number at about the 11th day. The presence of lipoid was regarded as evidence of increased cellular metabolism. In contrast it was found that lipoid occurs in the epithelium of the lower cervix and vagina only at oestrus and the appearances are those of fatty degeneration. After ovariectomy the lipoid disappears from the epithelium of the uterine horns in about 3 days and from the distal part of the uterine body in about 10 days (Snell and Nicol, 1955).

Nicol (1935) reported that lipoid can be produced experimentally in the uterine horns of the ovariectomized guinea-pig by the injection of corpus luteum hormone preceded by small sensitizing doses of oestrogen, but not by corpus luteum hormone alone.

Gilbert (1942) working on the castrate rabbit concluded in relation to endometrial lipoid that there is a delicate balance between oestrogen and progesterone and that the optimum lipoid appearances are found only when the correct balance between these hormones exists.

The present research was designed to reproduce experimentally the cyclic lipoid appearances in the genital tract of the normal guinea-pig. To ensure reliable comparison between the animals the hormone injections were timed so that any given day of the experimental oestrous cycle in the ovariectomized animal would correspond to the same day of the cycle had the ovaries been present. Thus the genital tract would, as far as possible, be subjected to the same hormonal influences from the pituitary and other endocrine glands as in the normal animal.

MATERIAL AND METHODS

Sixteen virgin guinea-pigs aged about one year were used in the investigation and all were known to have a regular oestrous cycle, as verified by the vaginal smear technique (Stockard and Papanicolaou, 1917; Selle, 1922). The animals were divided into five groups, 4 animals being double ovariectomized on the 3rd day of the cycle and 3 on the 6th, 9th, 12th and 15th days. For all the animals a time interval equal to two oestrous cycles (32 days) was allowed to elapse after ovariectomy to ensure complete recovery from the operation and the disappearance of the ovarian hormones from the blood.

Each animal was then given a course of daily intramuscular injections of oestrogen and progesterone for a period equal to one cycle (i.e., 16 days), the hormones being injected separately about the same time each day. The dose of each hormone was calculated jointly on the basis of the doses used in previous work on the guinea-pig and on the oestrogen and progesterone excretion levels in the urine of the human subject (Smith, Smith and Pincus, 1938; Venning

and Browne, 1937; Wilson, Randall and Osterberg, 1939). Two graphs were then constructed from which could be read off the daily doses of oestrogen and progesterone required for each animal (Fig. 1). To assist in the construction of the graphs we had found that large amounts of lipoid could be produced throughout the genital tract by the injection of 0·1 mg. of oestradiol benzoate daily for 6 days followed by 0·4 mg. of progesterone daily for 5 days. The largest doses of progesterone were planned to be given between the 5th and 11th days of the experimental cycle since the corpus luteum in the guinea-pig is fully formed by the 5th day of the cycle (Loeb, 1906) and begins to regress about the 11th day or soon after (Loeb, 1911).

The date of killing was arranged to correspond, had the ovaries been present, with the

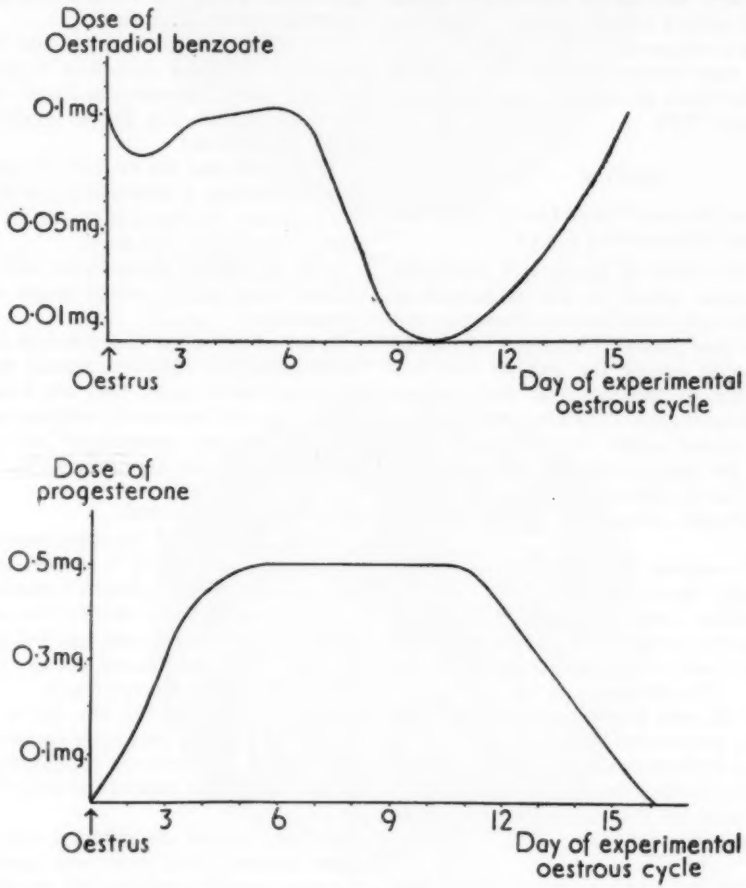

FIG. 1

Graphs showing daily dose of oestradiol benzoate and progesterone given intramuscularly for 16 days to 16 double ovariectomized guinea-pigs in the production of an artificial oestrous cycle. On the days when both hormones were given they were injected separately about the same time.

day of the cycle when the animal was double ovariectomized.

The animals were killed with chloroform and the whole uterus and vagina were removed. All the specimens were fixed in 10 per cent formalin and frozen sections 10 μ thick were made of the uterine horns, the upper and lower parts of the uterine body, the cervix and the vagina. The sections were stained with Sudan III for 15 minutes, then decolorized in 50 per cent alcohol and washed in distilled water. Haematin was used as a counterstain. High concentrations of alcohol were avoided as these may dissolve some of the lipoid (Kaufmann and Lehmann, 1929; Romeis, 1929).

Results

Amount and Distribution of Lipoid Throughout the Experimental Cycle

During the course of injections it was noted that the vagina opened in all the animals at what would have been the time of oestrus had the ovaries been present. The degree of vaginal opening varied among the animals and was probably due to the fact that each animal received the same dose of the hormones irrespective of its size and weight. Vaginal smears taken from 5 of the animals showed cells similar to those seen during the four stages of a normal oestrus although leucocytes tended to predominate.

In all the animals the uterus was of normal size or slightly hypertrophied.

The amount and distribution of lipoid throughout the experimental cycle is shown for the different parts of the uterus and the vagina in Table I. The differences in the amount of lipoid that did exist between the animals of the same group would seem to be accounted for by the natural differences among animals (Nicol, 1933) and by the fact that each animal received the same dose of the hormones. The lipoid appearances are as follows:

Uterine horns and proximal part of uterine body

At the 3rd day of the experimental cycle a very small amount of lipoid is present in the lining epithelium of the uterine horn and proximal part of the uterine body. The lipoid globules are of small size and are concentrated above and below the nucleus and there is no obvious concentration either at the mesometric or anti-mesometric side of the lumen. An occasional lipoid globule is present in the cells of the gland fundi.

At the 6th day the amount of lipoid in the lining epithelium increases slightly. The lipoid globules are slightly larger but remain concentrated above and below the nucleus. In one of the animals a small amount of lipoid is present in the epithelium of the gland fundi.

At the 9th day a moderate amount of lipoid is present in the lining epithelium in the form of fine and coarse globules distributed above and below the nucleus (Fig. 2). No lipoid is present in the gland fundi.

At the 12th day the amount of lipoid in the lining epithelium is diminished and at the 15th day is absent. No lipoid is present in the gland fundi at the 12th or 15th days.

In all the animals the epithelial cells lining the uterine lumen are of normal height or slightly elongated.

In the stroma of the endometrium a few large lipoid-containing cells are present throughout the experimental cycle. They are found principally in the zone between the stratum compactum and the stratum spongiosum and are most abundant at the 6th day of the cycle.

Distal part of uterine body

At the 3rd day of the experimental cycle a small amount of lipoid is present in the epithelium covering the villus-like processes of the endometrium and the distribution around the uterine lumen is fairly uniform. The lipoid is in the form of fine and coarse globules distributed evenly throughout the cytoplasm.

From the 6th to the 9th day a moderate amount of lipoid is present in the lining epithelium and the globules are concentrated mainly in the infranuclear zone of the cells (Figs. 3 and 4).

At the 12th day the epithelial cells contain a great number of fine and coarse lipoid globules but there is still a tendency for the lipoid to be more highly concentrated at the base of the cell.

At the 15th day the amount of lipoid in the lining epithelium is greatly reduced. It is present

FIG. 2

Photomicrograph of section of uterine horn of double ovariectomized virgin guinea-pig at 9th day of experimental oestrous cycle. The lining epithelium contains a moderate amount of lipoid in the form of fine and coarse globules distributed above and below the nucleus. The lipoid appears black in the photomicrograph. Stained Sudan III. ×500.

FIG. 3

Photomicrograph of section of distal part of uterine body of double ovariectomized virgin guinea-pig at 9th day of experimental oestrous cycle. The epithelium covering the villus-like processes contains a great amount of lipoid. The lipoid globules appear black in the photomicrograph. Stained Sudan III. ×200.

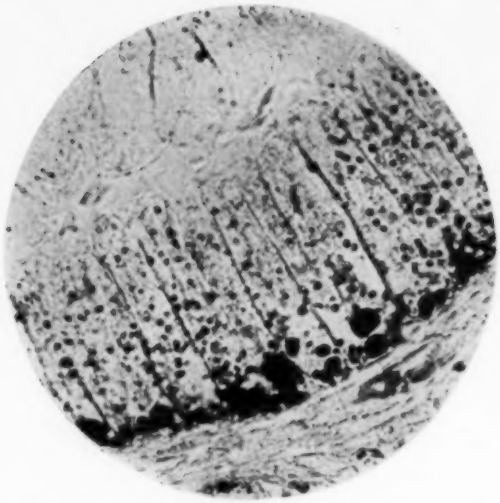

FIG. 4

Higher magnification of section shown in Fig. 3. The epithelial cells contain a great amount of lipoid in the form of fine and coarse globules which are concentrated mainly in the infranuclear zone of the cells. The lipoid appears black in the photomicrograph. Stained Sudan III. ×1200.

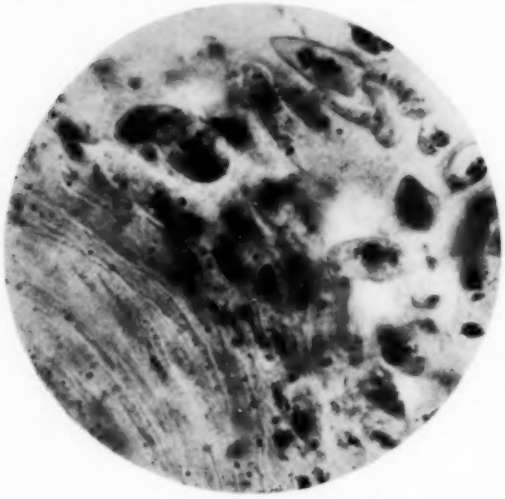

FIG. 5

Photomicrograph of section of vaginal wall of double ovariectomized guinea-pig at 12th day of experimental oestrous cycle. The epithelial lining is greatly thickened. The superficial cells contain coarse droplets of lipoid which appear black in the photomicrograph and many of the cells are being shed into the lumen. Stained Sudan III and haematin. ×600.

T.N., R.S.S.

TABLE I

Showing Amount and Distribution of Lipoid in the Epithelium of the Uterus and Vagina during the Experimental Oestrous Cycle in 16 Double Ovariectomized Virgin Guinea-pigs

Day of Experimental Cycle when Killed	No. of Animal	Uterine Horn	Proximal Part of Uterine Body	Distal Part of Uterine Body	Lower Part of Cervix	Vagina
3rd Day	190	−	−	++	−	+++
	185	−	−	++	+++	+++
	191	+	+	++	+++	+++
	197	++	++	+++	+++	++++
6th Day	152	+	+	+++	+++	++
	184	++	+++	+++	+++	+++
	146	++	++	++++		++++
9th Day	194	+++	+++	+++	+++	+++
	212	+++	+++	+++	++++	++++
	139	++++	+++	++++	+++	+++
12th Day	153	+++	+++	++++	+++	++++
	151	+	+	+++++	++++	
	161	+	+	++	+++	++++
15th Day	147	−	−	++		++++
	217	−	−	++		++++
	215	−	−	++	++++	++++

− = Absent. ++ = Small amount. ++++ = Great amount.
\+ = Very small amount. +++ = Moderate amount. +++++ = Very great amount.

mainly in the form of fine globules distributed throughout the cytoplasm.

Throughout the experimental cycle the villus-like processes of the endometrium were higher than normal, their branching is more complex and the covering epithelial cells are greatly elongated.

Cervix

The upper part of the cervix shows lipoid appearances similar to those in the distal part of the uterine body. In contrast the lipoid appearances in the lower part of the cervix are similar to those present in the vagina.

Vagina

Throughout the experimental cycle the epithelium is greatly thickened. The superficial cells contain a large amount of lipoid in the form of coarse droplets and many of the cells are in the process of being cast off into the lumen (Fig. 5).

DISCUSSION

Bourg (1929) working on the castrate rat found that the lining epithelium of the uterus contained many large fat granules and that they disappeared after the administration of small quantities of oestrogen.

Nicol (1935) reported that lipoid can be produced experimentally in the ovariectomized guinea-pig by the injection of corpus luteum hormone preceded by small sensitizing doses of oestrogen but not by corpus luteum hormone alone.

Van Dyke and Chen (1940) in the castrate monkey were unable by injections of oestradiol benzoate and progesterone to reproduce the amount of fat found in the normal uterus at the height of luteal activity. The fat however followed the same pattern as in the normal animal but in diminished amount.

Black, Heyns and Gillman (1941a, b) showed that the increased lipoid found in the luteal phase of the human menstrual cycle is not only dependent upon the metabolism of progesterone but also upon the metabolism of oestrogen which plays an equally important part in producing the balance required for optimum luteal effect.

Gillman (1941) found in the human endometrium that fat accumulated in the base of the gland cells between the 19th and 25th days of the cycle and then rapidly disappeared. He was of the opinion that at about the 25th day of the cycle the progesterone had produced its maximum effect and thus basal fat was present in a high percentage of cells; and that when the progesterone supply is cut off after the 25th day the basal fat rapidly disappears from the uterus. He thought this was probably due to absence or insufficiency of the progesterone. This view is supported by his description of the endometrium in the early months of pregnancy in which he found that during the period when the corpus luteum is known to be most active basal fat is present in the gland cells. He also found that the injection of 20 mg. of progesterone during the last week of the menstrual cycle increased the incidence of cells containing basal fat from 10 to nearly 100 per cent.

Gilbert (1942), working on the rabbit, reported on the distribution of lipoid in the genital tract at 8 and 12 days after castration. She found the presence of small globules of fat in the stroma cells of the endometrium and a diffuse distribution of fat in the surface epithelium. No fat was seen in the glandular epithelium. She also found in the castrate rabbit that it was possible to alter profoundly the distribution of lipoid by the administration of oestrogen or progesterone alone, or by oestrogen followed by progesterone, or by giving the hormones together. Her results showed that both oestrogen and progesterone when given alone tended to reduce the amount of fat in the epithelium and the stroma cells. Progesterone, however, differed from oestrogen in that it was capable of producing fat in the glandular epithelium. By giving oestrogen followed by progesterone in varying doses she found that the progestational response of the endometrium was increased but the basal fat in the glands remained unchanged. On the other hand, when oestradiol benzoate and progesterone were injected together in varying doses following previous sensitization with oestradiol benzoate it was found possible to produce numerous fine globules of fat in the glandular epithelium and large quantities of stroma fat. She concluded that the production of the normal lipoid appearances in the glandular epithelium and stroma cells is dependent not only on pretreatment with oestradiol benzoate but also on the optimum metabolism of oestradiol benzoate and progesterone thereafter. She was also of the opinion that the appearance of coarse globules of lipoid, larger than normally seen, in the epithelium and stroma indicated an inhibition of progesterone response and is related to an unfavourable metabolism of oestradiol benzoate and progesterone.

The results of the present research show that lipoid appearances closely comparable with the normal can be produced experimentally in the cells of the lining epithelium of the uterine horns and proximal part of the uterine body 32 days after ovariectomy by injecting varying doses of oestrogen and progesterone. The amount of lipoid in the lining epithelium did not fall however at the 6th day of the experimental cycle as in the normal animal. In the light of Gilbert's work on the rabbit the fall in the normal animal is probably due to an altered balance between oestrogen and progesterone at that time of the cycle.

The greatest number of large lipoid-containing reticulo-endothelial cells in the stratum compactum was present at about the 6th day of the experimental cycle compared with the 11th day in the normal animal (Nicol and Snell, 1954).

The present results also show that lipoid appearances closely comparable with those in the normal animal can be produced experimentally in the lining epithelium of the distal part of the uterine body. The coarse lipoid globules seen at the 12th day of the experimental cycle were much larger than normal and together with the hypertrophy of the villus-like processes suggest that the doses of the hormones given were excessive.

Throughout the experimental cycle the lower cervix and vagina showed lipoid appearances similar to those found in the normal animal at oestrus. The persistence of these changes throughout the experimental cycle indicates that the amount of oestrogen administered was greater than normal.

The disappearance of the vaginal closure membrane at the time of oestrus in the experimental animal is to be expected, since this is known to occur at oestrus in the normal animal (Stockard and Papanicolaou, 1919). The membrane probably re-forms in response to the falling concentration of oestrogen or because the metabolic activity of the oestrogen is impaired by the rising concentration of progesterone.

The present investigation therefore shows that in double ovariectomized guinea-pigs the cyclic lipoid appearances in the normal uterus can be reproduced fairly accurately by the injection of varying doses of oestrogen and progesterone, and that the lipoid in the uterine epithelium appears to be an index of metabolic activity dependent on the balanced action of oestrogen and progesterone.

Summary

(1) Lipoid was produced experimentally in the lining epithelium of the uterus in 16 double ovariectomized guinea-pigs by the injection of oestrogen and progesterone.

(2) By varying the doses of oestrogen and progesterone the normal lipoid appearances in the uterus during the oestrous cycle were reproduced fairly accurately in double ovariectomized guinea-pigs.

(3) The lipoid in the cells is believed to be an index of metabolic activity dependent on the balanced action of oestrogen and progesterone.

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ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At the Meeting of Council held in the College on Saturday, 21st May, 1955, with the President, Sir Arthur Gemmell, in the Chair, the following were elected to the Council to fill Statutory vacancies:

As representatives of the Fellows:

John Francis Cunningham, Dublin.
Thomas Norman Arthur Jeffcoate, Liverpool.
Harold Jordan Malkin, Nottingham.
John Harold Peel, London.

As representatives of the Members:

James Gerard Gallagher, Dublin.
Thomas Loftus Townshend Lewis, London.
Samuel Douglas Loxton, Bristol.

The following were admitted to the Fellowship:

Donald Rose Beaton.
Robert Kenneth Bowes.
Johannes Cornelius Coetzee.
Mary Doreen Daley.
Laurence Llewellyn Davey.
Ian Donald.
Archibald Sutherland Duncan.
Howard Roderick Duval.
Amy Dhunjibhoy Engineer.
Robert Magnus Haines.
Ian MacGilchrist Jackson.
Donald Forsyth Lawson.
Arthur Alexander Moon.
Roland Nattrass.
John Clifford Newbold.
Robert Clarendon Percival.
Benjamin Henry Sheares.
Hugh Stirling.
Claude Whittaker Taylor.

The following were admitted to the Membership:

Robert Henry Obuabasa Bannerman.
David Barron.
Henry Robert Clifford Benny.
David Byron Brown.
Thomas Ian Cope.
Alan Cameron Coulthard.
Keith Douglas Drayton.
William Allan Webb Dutton.
Brian Alan Gavourin.
Herbert Samuel Gavourin.
Tara Sankar Ghosh.
Antony Plumer Brunyee Harston.
Josephine Mary Reeve Heber.
Beryl Overton Howie.
Paul Ellis Jeffery.
Beryl Mary Joles.
Gerald Woolf Korn.
Wendy Ellen Lewington.
John Dilwyn Llywelyn-Jones.
Philippa Mary Ludlam.
John Gordon Mathie.
Appuahandy Ariyaman Mahanama Mendis.
David Methuen.
Catherine Hutcheon Mitchell.
Nanda Gopel Mukherjee.
Rathindra Nath Nag.
Richard Tankard Sears.
Harendra Bahadur Sinha.
David Henry Kenneth Soltau.
Arthur Edwin Medlock Stevenson.
Oswald Selwyn Treisman.
Yin-Kai Tsao.
John Kitching Tully.
Jacobus Adolf Mangold Van Belkum.

Dr. A. M. Sutherland was appointed William Blair-Bell Lecturer for 1955.

Professor Louis Hellman of the State University of New York was appointed Green-Armytage Lecturer for 1956.

The following were successful in the recent **Diploma in Obstetrics** examination:

Jessamine Mary Akhurst.
James Alexander.
Harry Cochrane Allen.
Anne Johnston Anderson.
Michael John Barnard.
Carl Theodore Herzl Barrett.
Renuka Basu.
Arthur Graham Blyth.
James George Blyth.
Beryl Mary Bromham.
John Wallace Brown.
Jane Buchanan.
Colin Deas Campbell.
Margaret Ethlin Chitty.
Alan Roger Chrispin.
Elinor Betty Clark.
Priscilla Anne Clark-Maxwell.
John Sunderland Clayton.
Elinor Margaret Cleland.
William Maurice David Clements.
Mary Clothier.
William George Cooke.
Robin Leslie Coppock.
Douglas Cecil Cornish.
Florence Mavis Cousley.
Philip Harben Crosskey.
Lois Ruth Davidson.
David William Davis.
David Alfred De Renzy-Martin.
Gerald William Donaldson.

Dale Miller du Toit.
Charles Edward Elliott.
Constance Hope Ellis.
Lucy Malins Ellis.
Emyr Wyn Evans.
Joan Maray Evans.
Julian Richard Eve.
Hugh Thomas Fay.
Helena Mary Fehily.
Graham Findlay.
Kathleen Teresa Flanagan.
John McColl Forrester.
Raymond William Galloway.
William Forbes Petrie Gammie.
Richard Ean Morton Geldart.
John Alan Gibson.
Richard Malcolm Goddard.
Hugh Richard Gompertz.
John Richard Gough.
Sheila Mary Gough.
John Leonard Graham.
Fred Vivian Griffiths.
Arthur Barrie Guest.
Alastair Turner Gray Gunn.
Edwin Aldridge Haddock.
Hugh Nevill Hardy.
Adeline Kwee-Hong Heah.
John Heffernan.
Robert Manley Hodges.
William Strachan Hossack.
David Sidney Iles.
Katherine Isobel Jack.
Elizabeth Mary Jennings.
Anthony Harold John.
Isabel Doreen Johnson.
Vivian Kathlyn Jones.
Alexander Reid Jordan.
Kevin Kelly.
Alexander Shearer Lovat Kennedy.
Esther Selkirk Kerr.
Bernard Kirsch.
William Lang.
Laurence Alfred Lees.
Charles Stuart Leithead.
Harry Colquhoun Leslie.
Eldred Reginald Lester.
Norman Hunter Logan.
Peter Los.
Robert Hugh Mackay.
Bernard Norman McAdam.
Kathleen Mary McCartie.
Doreen Elizabeth McConnell.
Willy Eduard Hendrick Maeckelberghe.
John Michael Manners.
Muriel Jean Martin.
John Francis Amor Maskell.
Harry McIntosh Morgan.
Eleanor Morrison.
Mary Joan Mossman.
Kenneth Arthur Naylor.
Margaret Ann Norman.
Jean Mary North.
John Whitehouse Parkin.
Rena Elizabeth Partridge.
William Frederick Paveley.
John Allan Payne.
Mary Phillips.
Henry Ronald Playfair.
Thomas Alfred Plumley.
John Gerald Powell.
Elizabeth Mary Price.
Mervyn Niblett Prichard.
Margaret Joy Purser.
Olga Mavis Rampersaud.
Amla Rama Rao.
Antony Maxwell Reader.
Denzil Mervyn Reader.
Evan Glyn Rees.
Hans Friedrich Reichenfeld.
Rosalind Mary Rewcastle.
David Powys Wynn Roberts.
Margaret Joan Lynn Robinson.
Robert Samuel Boulderson Rogers.
Joseph Neville Roper.
Albert David Rowlands.
Hilary Marion Rowson.
Margaret Cleland Russell.
Dorothy Sanderson.
Thomas Allan Sanderson.
Kenneth Scott.
Robert William Scott.
Jane Margaret Scott-Brown.
Jean Mary Shields.
Martin Jocelyn Sill.
Henry Roy Simpson.
William Sugley Sinton.
Geoffrey Hugh Smerdon.
Richard Ian Smith.
John Horton Spurway.
Raymond Mark Stanford.
Hilary Kathleen Ross Steen.
Phyllis Annette Stevens.
Audrey Beryl Stevenson.
Dan Stewart.
James Stewart.
Thomas Frederick Stoyle.
Heather Barber Thompson.
John Thompson.
David Tingle.
Annemarie Dora Tupper.
Jack Walker.
Patricia Gwendoline Wallis.
William Warren Watson.
John William Stuart Webb.
James Ronald Welsh.
Beverley Frederick Whiteley.
Sheila Wightman.
Gladys Mary Harriet Williams.
John Reginald Wood.
William James Wright.
William Owen Collingwood Young.

REPORTS OF SOCIETIES

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

January 1955

The Annual General Meeting of the North of England Obstetrical and Gynaecological Society was held in Manchester on 21st January, 1955. The following were elected Officers for 1955.

President—Mr. H. J. Malkin (Nottingham).

Vice-Presidents—Dr. K. V. Bailey (Manchester), Mr. T. E. Lennon (Liverpool), Mr. H. Agar (Leeds), Mr. N. L. Edwards (Sheffield), Mr. D. F. Smith (Newcastle).

Hon. Treasurer—Mr. C. H. Walsh (Liverpool).

Hon. General Secretary—Mr. J. B. Cochrane (Nottingham).

Hon. Reporting Secretary—Miss U. M. Lister (Leeds).

Three Honorary Fellows of the Society were elected—Dr. J. M. Bride, Dr. C. M. Hibbert, and Dr. T. E. Walker.

Miss C. Bates reported

An Unusual Caesarean Section

The patient was a healthy girl of 23 who had attended an antenatal clinic regularly. As the foetal head was still high at the 36th week, pelvic examination was undertaken and a tumour discovered filling the pelvis. Miss Bates saw the patient for the first time 1 week later, and after confirming the findings planned to admit the patient for Caesarean section and removal of the tumour near term. At operation on 8th March, 1954 the lower segment of the uterus was found to be poorly formed with tortuous vessels on the surface. The peritoneum was incised and Miss Bates then made a small incision in the lower uterine segment. She encountered much bleeding and the muscle seemed very thick. Owing to this a finger was inserted into the incision and the uterus pulled upwards and the incision deepened to the membranes and then widened with the fingers. The baby was then delivered.

During delivery of the placenta Miss Bates noticed that the upper edge of the incision was V-shaped and at the apex there was a circular structure with a hole at its centre. Exploration revealed no cervical canal in its normal position, but a similar structure was then discovered in the lower edge of the incision. The ovarian tumour was then removed to facilitate suture of the uterus and, after passing a tube through the two ends of the severed cervix, the edges were united with interrupted sutures and the muscle on either side repaired in 2 layers. The appearance after covering with pelvic peritoneum seemed that of a normal lower segment Caesarean section.

Vaginal examination after the operation showed the cervix high up under the symphysis. Recovery was uneventful.

She reported 6 weeks and again 4 months later when normal menstruation had been resumed. A salpingogram at this time showed on the first two films normal uterine and tubal outlines, but on the third film a shadow on the left which Miss Bates thought might be a fistula from the suture line. Further progress has been uneventful.

Discussion

Dr. R. Newton thought that the shadow in the third X-ray might be an artefact.

Mr. J. K. Wilson reported that he had recently been performing hysterograms 3 to 6 months after Caesarean section and an effusion into the broad ligament at the site of the uterine incision was not uncommon.

Mr. S. Bender asked if this could be a sacculation of the anterior uterine wall.

Miss Bates replied.

Mr. S. B. Herd described a case of

Recurrent Puerperal Arterial Occlusion

The patient had no past medical history and there had been 3 normal deliveries, but the 4th had been complicated by accidental ante-partum haemorrhage and severe anaemia.

The 5th pregnancy occurred in 1952, and was normal except for headache and oedema in the last month. Spontaneous, uncomplicated delivery occurred in hospital and no ergot preparation was used. Progress was normal until the 6th day when she noticed pain in the left foot. Next morning, when she complained of this, there was discoloration of the foot and lower third of the leg. The foot was cold, but there was no swelling or loss of power. Pulsation was not felt in the dorsalis pedis. A diagnosis of arterial occlusion, probably in the popliteal artery, was made, but no source of embolus was found and there was no pyrexia. Treatment with Priscol 25 mg. 8-hourly, anticoagulants, penicillin and exposure of the affected limb was commenced. There was rapid improvement and by the 10th day it was evident that only the great toe would be affected. Later localized gangrene developed and the terminal and proximal phalanges were removed. An arteriogram showed no sign of occlusion of the femoral artery or its branches.

The 6th pregnancy occurred in 1953, and the patient was admitted in labour, but she had not been seen in the antenatal period. Labour was again normal and the puerperium uncomplicated until the 6th day, when again signs developed, this time in the left hand and arm. The index and little fingers were most severely affected, the radial pulse was not palpable, the ulnar doubtful, but the brachial pulse in the antecubital fossa was normal. Twenty-four hours later Mr. Herd found loss of sensation over the middle fingers, cyanosis of the index and little fingers, and pink discoloration of the 2nd and 3rd

fingers. Movements of fingers and hand were normal. Blood count and Wassermann reaction were normal. Treatment with Priscol, penicillin and anticoagulants again resulted in rapid improvement and the radial pulse returned feebly 3 days later. By the next day, the hand and arm had recovered except for the two fingers which showed superficial necrotic areas, and eventually pus was released. Two months later there was still coldness in the hand and pain on immersion in cold water.

The last reference in the literature that Mr. Herd could find came from Mair (1943) of Aberdeen who described a fatal case, collected 110 cases from the literature and added a further 13. Of these 13 new cases, 11 were fatal, 1 followed abortion, 1 after ruptured ectopic pregnancy and 1 was associated with *Clostridium welchii* infection. Of the total 124 cases sepsis was frequently present, and ergot preparations were responsible in 25 cases, and the gangrene affected the lung, vulva and perineum as well as the limbs. The condition is rare, only 1 case having occurred in 148,000 deliveries in a 10-year period in the London County Council area. Pyrexia is the rule in these cases and an extragenital focus of infection may be present, but Mair reached no definite conclusion as to causation.

Mr. Herd found that no recurrent cases of arterial occlusion have been described. In his case no ergot preparation had been used, and there was no clinical evidence of infection though blood culture showed a staphylococcus after the second occlusion. Whether the actual lesion in the vessels was spasm or embolus had not been established but embolus was not likely. Mr. Herd thought that local arterial spasm might provide an explanation, with an alternative of thrombosis favoured by infection. Treatment in Mr. Herd's case was relatively simple, but he mentioned the possibility of embolectomy, sympathetic nerve block or even amputation.

Reference

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Discussion

Dr. E. Parry-Jones had seen a similar case in a multiparous patient. Labour was normal, there had been no infection, and the signs in the right arm resolved with anticoagulant therapy.

Professor W. I. C. Morris said that two processes might be involved; occlusion of a major artery and arteriolar spasm. Pallor and coldness occurred in the early stages of deep venous thrombosis and good results could be obtained with novocaine block. Arterial embolus could occur without it being possible to find its origin. He had seen a case in which an embolus had been removed from the bifurcation of the aorta after ectopic gestation, and the patient had recovered.

Miss U. M. Lister read a short paper on

Ruptured Uterus

Ruptured uterus is one of the more unusual obstetric catastrophes, and its incidence has been reported as less than 1 in 1,000 cases by authors in America and Europe (Eastman, 1945; Lynch, 1945; Morrison and Douglass, 1945), Brierton (1950), found that since 1918 the incidence of ruptured uterus had not decreased appreciably mainly because of the rising frequency of rupture of Caesarean section scars. The causes of rupture of the uterus he divides into 3 groups; rupture of a uterine scar, trauma during operative delivery and spontaneous rupture, and the 5 cases to be reported fall into this last group. During the 2 months in which they occurred 521 patients were delivered in the hospital at Ibadan, making an incidence of 1 in 104 cases.

The first patient was found to be in a state of shock during the routine labour ward visit. She was a woman of about 30 years who had had 6 vaginal deliveries. She received no antenatal supervision, and labour commenced spontaneously, the membranes rupturing soon after. Nine hours later, as she had not been delivered and foetal movements had ceased, she made her way to hospital, and at that time her condition was good.

When seen for the first time by the medical staff, 8 hours later, there was evidence of shock. The abdomen was tender and distended. The foetus could be felt with the head presenting at the pelvic brim and no foetal heart was heard. Vaginal examination revealed moderate blood loss, the head still above the pelvic brim and a vertical tear in the posterior wall of the uterus.

There was some delay before laparotomy could be performed as the theatre was in use. Blood transfusion was set up, and when the operation was commenced about 2 pints of blood were found in the peritoneal cavity with the placenta which had been extruded through the tear. As the foetus was *in utero* the tear could not be exposed and the uterus preserved. A 6 pounds 13 ounce baby was extracted and hysterectomy performed. At the time of the operation the patient's condition was poor and the transfusion was continued throughout the day. A.T.S. and A.G.G.S. were given in addition to penicillin, but there was gradual deterioration and she died early next morning.

While waiting for the theatre for the previous case, a taxi was seen to draw up and a very ill-looking woman was helped out. She was said to be 30 years old and had delivered 3 children normally. She had sought no antenatal care, and at 2 p.m. on 24th June labour commenced. Since that time she had been bearing down but there had been no vaginal bleeding. Her condition was desperate. She showed extreme pallor of the conjunctivae; her temperature was 102° and pulse and blood pressure were so feeble, neither could be recorded. There was slight abdominal tenderness and the foetus could be felt apart from the uterus.

Transfusion was set up and arrangements made to find donors, but it was 2 hours before laparotomy could be commenced. The baby and placenta with much blood were found free in the peritoneal cavity, and a long tear extended right across the posterior lower segment. Suture was impossible, and hysterectomy was performed. By the end of the operation her blood pressure was 80/40 and pulse 130. A.T.S. and penicillin were given, and more blood obtained, but there was never improvement, and death occurred 18 hours after operation.

Four days later a woman of 30 years, who had had 3 normal deliveries, was brought to the hospital at 8 p.m. She had obtained no medical care during the antenatal period and labour had commenced at 6 that morning. One hour later the membranes had ruptured and there was slight vaginal bleeding. Medicine of unknown type had been administered both orally and per vaginam to such effect that there was gross oedema and a catheter could not be passed. Her condition was poor, the pulse was rapid and the blood pressure difficult to obtain. A diagnosis of ruptured uterus was made, the foetus being felt free in the upper abdomen.

A blood transfusion was set up, and at laparotomy a 7½ pound foetus was removed from the peritoneal cavity where there was much free blood. Attempts to repair the tear, which again was across the posterior lower segment, were unsuccessful as the stitches cut out, and hysterectomy was performed. The transfusion was continued; A.T.S. 3,000 units and penicillin were given, and there was gradual improvement though a temperature of 100 to 102° was sustained for several days. Eight days after operation a foot drop was discovered, and later the temperature again rose, but despite this the patient wished to go home, and she was not seen again.

After an interval of 4 days a parous woman of 25 whose 2 children were still living, was admitted to hospital at 11.30 p.m. Labour had commenced 12 hours before admission, the membranes had ruptured at the onset, but there had been no vaginal bleeding. The patient was cold and shocked when first seen, with a feeble rapid pulse. Blood transfusion was commenced and laparotomy confirmed the presence of much blood and the foetus free in the peritoneal cavity. The tear extended right across the anterior wall of the lower uterine segment and there was a large retroperitoneal haematoma on the left. Hysterectomy was performed, and immediately after the operation aureomycin in the transfusion and A.T.S. were given as there was evidence of peritonitis, but, though the blood pressure rose, the patient collapsed and died 24 hours after operation.

It was 9 days later that the last patient in this short series was admitted to hospital. She was 22 years old and had 1 living child. Labour had been in progress 8 hours and during the last 4 hours there had been constant slight vaginal bleeding. Her condition was good when admitted, but 5 hours later, when she became restless and pale and the blood pressure fell, medical aid was called. The abdomen was then found to be distended and there was a grossly hydrocephalic foetal head at the pelvic brim. A transfusion was commenced with plasmosan until blood was available. Vaginal examination under anaesthesia showed that, in addition to the hydrocephalic head, there was a tear in the posterior lower uterine segment. It was felt that matters would be simplified if the head was perforated per vaginam. Willett's forceps were then applied to the skull through the perforation and by traction a 5 pound baby was delivered. The placenta followed at once. Laparotomy was then undertaken and the tear found extending obliquely across the posterior wall of the lower segment, with a large haematoma behind the descending colon. Hysterectomy was performed, and the cervix oversewn with some difficulty owing to its oedematous state. At the end of the operation the blood pressure was still low, but it rose gradually with further transfusion. There was a high temperature for the first 2 days but later recovery was uneventful, and the patient left hospital on the 10th day after the catastrophe. She was much distressed 2 weeks later when she came to the hospital to find that further pregnancies were impossible.

The classical signs of rupture of the uterus have been given by Brierton (1950) as shock, constant pain, cessation of uterine contractions and vaginal bleeding, but Morrison and Douglass (1945), in a series of 45 cases, reached a diagnosis in only 23 before death. In the 5 cases presented here, shock was severe in all and 3 showed slight vaginal bleeding, but the history of pain was difficult to obtain. The diagnosis was established by abdominal examination in the 3 cases where the foetus had left the uterus and, in the remaining 2, careful investigation of severe shock led to the detection of the tear during vaginal examination.

These were all young patients, who had had few children, and in none had labour been unduly prolonged. Hydrocephaly in one case, and in the rest dystocia due to moderately large babies, led to the uterine rupture, which in 1 was situated anteriorly, and in the other 4 in the posterior lower uterine segment. Immediate laparotomy is the treatment of choice, though, in the case of the patient with the hydrocephalic foetus, perforation and easy extraction of the child were first undertaken at the time of the vaginal examination. Lynch, however, advises against delivery of the child per vaginam should it still be in the uterus. Repair of the tear and sterilization may in some cases be feasible, but when it was tried in this series retroperitoneal bleeding and oedema of surrounding structures made suture impossible. Hysterectomy was, therefore, done in each case, and as much blood as was available and antibiotics were administered. Spontaneous rupture of the uterus causes a mortality higher than that due to rupture of a uterine scar, death being due mainly to haemorrhage and infection, and reaching nearly 50 per cent of cases. It is only with adequate antenatal care, immediate operation, correction of blood loss and control of infection, that this figure can be reduced.

References

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Eastman, N. J. (1945): *Amer. J. Obstet. Gynec.*, **49**, 529.
Lynch, F. J. (1945): *Amer. J. Obstet. Gynec.*, **49**, 514.
Morrison, J. H., and Douglass, L. H. (1945): *Amer. J. Obstet. Gynec.*, **50**, 330.

Discussion

The President emphasized how insidious the signs may be at the onset, though in some cases the rupture of the uterus may present with dramatic speed.

Mr. A. C. H. Walker (Manchester) said that in the 3 years he had been in Ibadan he had seen only 23 cases, and the fame of the hospital must have spread. Of these 23 patients 16 died; 18 were unbooked, only 3 of these

surviving. Four cases were of interest: the first patient was in labour 6 days when she noticed a severe pain and collapsed. Two years later the foetus was removed from the abdomen. The second patient developed a rupture at the cervico-vaginal junction with the foetal head in the vagina. Vaginal hysterectomy was done but she died from secondary haemorrhage. The third case was similar. The fourth case was delivered at home and admitted because of severe shock, when on opening the abdomen the tear was found concealed by adhesions and was not repaired. Later she became pregnant again, but at Caesarean section no sign of the scar or adhesions could be found. Mr. Walker had seen cases of ruptured uterus in young primiparae, and thought that the native medicine these patients were given contained an oxytocic factor.

Miss C. Bates (Nottingham) reported a case she had under her care at that time. The patient was 28 years of age and in her third pregnancy. She developed constant pain near the end of the first stage in labour, and was admitted to hospital 24 hours later. At that time she had severe abdominal pain, shoulder tip pain and the foetal limbs were felt easily. She is now making a good recovery after suture of the tear in the anterior uterine wall. The baby weighed 9 pounds 5 ounces.

Mr. R. H. J. M. Corbet (Preston) showed tables of his cases and reported a lower mortality since 1929 when laparotomy had been undertaken at once. Eleven of the 38 cases were after operation on the uterus.

Mr. C. J. K. Hamilton (Liverpool) reported a case.

Mr. C. H. Walsh (Liverpool) thought the word "spontaneous" should not be employed as all were multiparae. He mentioned a case of uterine rupture after perforation at curettage.

Mr. J. P. O'Dwyer read a paper on

ACUTE IDIOPATHIC PORPHYRIA COMPLICATING PREGNANCY

(This article appears on page 437 of this issue)

Discussion

The President, commenting on the rarity of this condition, said that the physicians in his area met acute porphyria about once in 3 years.

Mr. E. L. Nicholson (Carlisle) had seen 1 case in whom the acute attacks were precipitated by menstruation.

HOSPITAL REPORTS

BY

ANTHONY W. PURDIE, M.B., F.R.F.P.S., F.R.C.O.G.

CLINICAL REPORTS OF THE MATERNITY DEPARTMENT, GUY'S HOSPITAL, LONDON, FOR THE YEARS 1951 AND 1952

IN these reports cases are divided into two categories, Class A and Class B. Class A includes all patients living in the Guy's Hospital Maternity District, which is a very compact district, whether delivered in their own homes or in the hospital and whether or not they have attended the antenatal department during their pregnancy. Class B includes all other patients. It is claimed that Class A represents the unselected midwifery practice of this very circumscribed district. When this classification was introduced the hospital was responsible for practically all confinements in the area, but now is responsible for only two-thirds of the confinements. Of the cases in the reports 80 per cent are Class A and 20 per cent class B.

During these 2 years the hospital was responsible for 2,228 deliveries. There were 3 maternal deaths; in each, death was due to pulmonary embolism occurring on the 9th, 30th and 40th days respectively.

There is a useful table in each report showing a summary of results in Class A and Class B separately from the year 1928.

ANNUAL REPORT FOR THE YEAR 1952. DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, UNIVERSITY OF OTAGO, NEW ZEALAND

THE obstetric work is carried out in the Queen Mary Maternity Hospital and in Miller Ward, Dunedin Hospital, and the gynaecological work is carried out in Batchelor Ward, Dunedin Hospital. The maternity cases come partly from local bookings and partly from emergency admissions from an area up to 100 miles distant from Dunedin.

Maternity admissions numbered 772, among which there were 748 deliveries. There were no maternal deaths; the stillbirth rate was 29 per 1,000 total births and the neonatal death rate 14 per 1,000 live births. The Caesarean section rate was 4·9 per cent, and the forceps rate 3·9 per cent.

The number of cases dealt with is small but the material dealt with and the picture presented is similar qualitatively to that of larger units.

There were 700 gynaecological admissions. Major operations numbered 249, minor operations 332 while in 119 cases investigations were carried out or treatment was conservative.

REPORT OF THE OBSTETRICAL AND GYNAECOLOGICAL CASES FOR THE YEARS 1949 AND 1950, FACULTY OF MEDICINE, UNIVERSITY OF CEYLON

THESE two reports are similar; each runs to some 50 pages. Each consists of detailed figures of gynaecological and antenatal out-patient attendances, of diseases of the various genital organs and the various gynaecological operations performed. Then follows a list of deaths with a few words of description of each fatal case. In turn there follow tables showing some single case data of (1949) breech deliveries, rare conditions, heart, placenta praevia, ante-partum haemorrhage—accidental, hydramnios, face, retained placenta, puerperal fever, post-partum haemorrhage, forceps deliveries, Caesarean section, A.P.H. uncertain origin, syphilis, abortions and miscarriages, twins, stillbirths, pre-eclampsia, and anaemia. There is no preface or critical survey, the number of beds is not given nor any information about the hospital (the name of which is not given) where the work is done.

In 1949 there were 2,176 gynaecological admissions and 1,074 gynaecological operations were performed and there were 900 obstetric admissions with 661 deliveries. In the list of deaths 22 cases are recorded but gynaecological and obstetric deaths are not shown separately. The information given about these is inadequate, e.g., "pelvic peritonitis—paralytic ileus"; whether she was pregnant or not is not stated.

It is doubtful if in the single case data tables all cases of the condition are shown. For example, in the placenta praevia table only 2 cases appear: the mother lived in each case, but in the list of deaths earlier in the report a maternal death from septicaemia following Caesarean section for placenta praevia is recorded. Twelve Caesarean sections are detailed in the Caesarean Section table, but the fatal case just described does not appear in it. In the abortion table 5 cases appear (in none is the result to the mother recorded) yet earlier in the report it is said there were 311 abortions. The reason for this kind of selection is not clear.

There are many minor errors. CHCL 3 is repeatedly used to indicate chloroform, Cephato-pelvic disproportion appears frequently, other spelling mistakes are common while a number of unusual abbreviations are

used and these are not shown in the list of abbreviations.

These reports hardly conform to the standard expected in University publications.

CLINICAL REPORT OF THE MATERNITY DEPARTMENT, PADDINGTON GENERAL HOSPITAL, FOR THE YEAR 1952

ADULT admissions during the year numbered 2,141 and among these were 1,927 deliveries. There was not a maternal death during this period. The stillbirth rate was 18·3 per thousand live and stillbirths and the neonatal death rate 17·8 per thousand live births. The forceps rate was 5·3 per cent and the Caesarean section rate 2·7 per cent: 21 per cent of the sections performed were classical in type. There was no lack of serious or potentially serious cases. The staff are to be congratulated on a successful year's work.

LIVERPOOL MATERNITY HOSPITAL. REGISTRARS' REPORTS FOR THE YEARS 1950 AND 1951

DURING these 2 years there were 5,973 deliveries in the hospital with 5 maternal deaths. In 2 cases death occurred under anaesthesia for repeat Caesarean section; in each case vomiting would appear to have been a significant feature. In another case following Caesarean section for marked essential hypertension deterioration set in rapidly 4 hours after satisfactory recovery from anaesthesia; autopsy was refused. The 2 remaining deaths were due respectively to eclampsia and rheumatic carditis with congestive failure. If an attempt is made to classify these deaths the first 2 would appear to have been avoidable, the third probably avoidable, the fourth technically avoidable but unavoidable as far as the hospital was concerned, while the last seems to have been unavoidable. The stillbirth rate during the period was 32·6 per 1,000 total births and the neonatal death rate 15·4 per 1,000 live births.

The Caesarean section rate was 10 per cent and the forceps rate 12·3 per cent. There were 133 uncomplicated breech deliveries with 1 stillbirth (0·7 per cent) and 3 neonatal deaths (2·3 per cent) giving a total foetal loss of 3 per cent. During the 2 years there were 76 cases (1·3 per cent) of genital tract infections.

These carefully prepared reports also contain a very comprehensive paediatric section.

CLINICAL REPORT OF QUEEN CHARLOTTE'S MATERNITY HOSPITAL, LONDON, FOR THE YEAR 1951

THERE were 2,701 deliveries in the hospital during the year with 1 maternal death, a stillbirth rate of 27·3 per 1,000 total births, and a neonatal death rate of 19·7 per 1,000 live births. On the district there were 599 deliveries without a maternal death.

The hospital death was due to post-partum haemorrhage. At the 32nd week of pregnancy rapid spontaneous delivery of one stillborn and one live baby occurred one hour after the patient's admission, the placentae were delivered spontaneously followed by a large and well organized retroplacental clot. While the uterus contracted satisfactorily at first atonic haemorrhage commenced during the next hour. Ergometrine and pitocin were given without effect, blood transfusion was set up and in all she received 14 pints in 9 hours, packing of the uterus failed to control the bleeding, hysterectomy was performed 5 hours after delivery and, while there was transient improvement in her condition, deterioration set in followed by death 12 hours after delivery.

A 5-year table of comparative statistics shows a gradual rise in both the Caesarean section rate and the forceps delivery rate. In 1951 these were 4·3 per cent and 13·0 per cent respectively. The stillbirth rate has remained fairly constant over the past 5 years while the neonatal death rate for 1950 and 1951 shows considerable improvement over the 3 previous years.

The paediatric section of the report is designed to bring out the incidence and character of mortality and morbidity in the hospital period. Modern treatment of bacterial infections and advances in the diagnosis and treatment of neonatal conditions amenable to surgery have improved the outlook for all newborn babies able to survive the first 48 hours. Out of 53 neonatal deaths only 12 occurred after this time; almost as many (10) had died in the first hour. The point is made that in rhesus incompatability exchange transfusion does not solve all the problems of treatment.

MEDICAL AND CLINICAL REPORT OF THE WOMEN'S HOSPITAL, MELBOURNE, FROM 1ST JULY, 1952, TO 30TH JUNE, 1953

THIS is the first report from the Women's Hospital in which the Obstetric Section of the Report follows that suggested by a Committee of the Royal College of Obstetricians and Gynaecologists. A few of the tables have been summarized, e.g., those on pre-eclampsia, essential hypertension and chronic nephritis, external version, and forceps. Other tables have been added: Pregnancy following Previous Vaginal repair, Rupture of the Uterus, Termination of Pregnancy under 28 weeks, and Erythroblastosis Foetalis and Rh Immunized Mothers. It is contemplated that in the next report individual cases will be shown in the Gynaecological Section as is at present done in the Obstetric Section.

This report is a monumental piece of work. It covers 6,894 deliveries (among which there were 5 maternal deaths) and 1,761 gynaecological in-patients and a large number of out-patients. The labour and care expended on it are reflected throughout the report which is decidedly worthy of study.

BOOK REVIEWS

"Vaginal Hysterectomy." By LAMAN A. GRAY, M.D., Associate Professor of Gynecology, University of Louisville Medical School. Pp. x+137, with 31 figs. 1955. Price 34*s*.

"Hysterectomy." By JOHN C. BURCH, M.D., F.A.C.S., Professor of Gynecology, and HORACE T. LAVELY, M.D., Instructor in Gynecology, Vanderbilt University School of Medicine. Pp. 94, with 32 figs. 1954. Price 40*s*.

THESE two monographs are recent additions to the series of American Lectures in Gynecology and Obstetrics, published by Charles C. Thomas in the U.S.A. and by Blackwell Scientific Publications in this country, and the typography and illustrations maintain the usual high standard.

Dr. Gray's book will probably have the wider appeal, for, by nature of its more limited subject, it provides greater depth and detail. The aim is to teach the successful performance of vaginal hysterectomy to the postgraduate in training and to the gynaecologist who only occasionally removes the uterus by this route. Dr. Gray, as any writer of a monograph, is an enthusiast on his subject, but he tempers his enthusiasm with discretion and wisely details the limitations of the vaginal approach. In addition to the standard operation, in which a modified Heaney technique is preferred for closure, the combination of vaginal hysterectomy with repair is fully described, with special emphasis on the cure of any enterocele and the prevention of its development subsequent to operation. It is pointed out that vaginal hysterectomy carries a low mortality, but that complications are neither infrequent nor unimportant and merit full discussion. A feature of this book is the historical review of the operation, complete with over 100 references, which accounts for more than one quarter of the total text.

The volume by Drs. Burch and Lavely is built round a series of over 1,200 consecutive hysterectomy operations without a death, already largely reported in the *Annals of Surgery*. The techniques of vaginal, and simple and radical abdominal hysterectomy are separately depicted with liberal descriptive legends to each illustration. A preliminary chapter on "An Approach to Hysterectomy" is an interesting essay in which the effects of the operation on ovarian and sexual functions are discussed. The aphorism is coined that in no other operation do the results depend as much on the pre-operative psychological state of the patient as on her post-operative physical state. This book makes pleasant reading of the views, methods and results of one team, but its value would be enhanced by the addition of a detailed account of pre-operative and post-operative care in both normal and complicated cases.

"Diseases Affecting the Vulva." By ELIZABETH HUNT, B.A., M.D., Ch.B. Fourth Edition. Pp. 236, with 47 illustrations and 17 plates in colour. Henry Kimpton, London, 1954. Price 31*s*. 6*d*.

THIS book by a dermatologist should be frequently consulted by the gynaecologist because it deals, as an expert alone can deal, with the many abnormal conditions of the vulva that are local manifestations of diseases common on other skin surfaces. Amongst these are seborrhoea, hyperidrosis, eczema, psoriasis, leucoderma, lichen planus, etc.

It is rather disturbing for the gynaecologist to find that the following varieties of lichen planus have been observed on the vulva: (1) lichen ruber planus, (2) lichen planus of mucous membrane, (3) lichen sclerosus vel atrophicus, (4) lichen planus bullosus, (5) lichen planus erythematosus and (6) lichen planus causing atrophy of hair follicles.

In a chapter devoted to external irritants the author reminds us of the vulvar irritation occasionally caused by therapeutic agents applied locally, such as cocaine derivatives (percaine, procaine) and antibiotics (penicillin, chloromycetin). In parenthesis the author points to the little known fact that cocaine applied in an ointment may lead to addiction. Another chapter deals with eruptions caused by drugs taken internally, e.g., antibiotics, sulphonamides, hypnotics, stilboestrol, etc. There are interesting sections on the relation between vulvar conditions and deficiency, endocrinal and metabolic disorders. Other chapters are devoted to neoplasms, parasitic and virus diseases and recurrent ulcers.

Perhaps the most interesting chapters for the gynaecologist are those in which the author discusses leucoplakia and kraurosis vulvae. She gives reason for the view that the description of these conditions common in British textbooks of gynaecology gives an incorrect impression of their essential pathology. She points out that the term "leucoplakia" was originally applied by Schwimmer in 1877 to the white patches present on mucous membranes, especially of the tongue, where they are more commonly seen in men after the age of 50, with a history of syphilis and often of excessive smoking. It has a special importance in that it occasionally passes over into malignancy. Dr. Hunt argues that by applying the term to the white patches occurring on the skin surfaces of the vulva and perineum Bonney had departed from the classification accepted by dermatologists and that he had thus confused the issue. She says: "A comparison of Bonney's histo-pathological findings in leucoplakic vulvitis with the histo-pathology of a lichen planus eruption terminating in sclerotic changes, i.e., lichen sclerosus . . . reveals the identity of the histopathology of leucoplakic vulvitis and of lichen sclerosus." Dr. Hunt believes that there is a distinctly greater risk of carcinoma developing from the true leucoplakia of the mucous membrane of the vulva than from the spurious leucoplakia of the skin surface. She quotes

Taussig's statement that antecedent "leucoplakic vulvitis" was present in 16 out of 21 cases of vulval cancer but this could not give any indication of the total risk which had to take account of those cases in which malignancy failed to develop. In 96 cases of lichen sclerosus, i.e., "leucoplakic vulvitis", observed by herself, cancer supervened in only 4.

Dr. Hunt furthermore believes that the atrophic changes which gradually develop in areas affected by lichen sclerosus, and which lead often to widespread secondary trophic changes in the mucous membrane as well as in the skin, result in the condition known as kraurosis. "Such observations point to the conclusion that kraurosis represents a late stage of lichen sclerosus of the vulva, i.e., leucoplakic vulvitis, as opposed to the view that leucoplakic vulvitis and kraurosis are distinct diseases."

The text of the book is illustrated by many excellent figures and a considerable number of beautifully reproduced colour photographs.

"A Review of the Proceedings of the International Congress on Gynaecology and Obstetrics, Geneva, July 26 to 31, 1954." Librairie de l'Univérsité, Georg, S.A. Price 80 Swiss francs.

THE publication of this large volume of more than 1,300 pages on the first day of the International Congress speaks most highly of the organizing ability of the Congress Committee and its Editors. There are 161 contributions on obstetrics and gynaecology ranging over a very wide series of subjects, and in reviewing this volume it is impossible to comment on the individual contributions. The theme of the Congress—"Prophylaxis in Obstetrics and Gynaecology"—is evident throughout. Thus, in dealing with cancer of the uterus the vast majority of the papers are concerned with early recognition and the treatment of the early case. However, it is surprising that the prophylaxis of genital prolapse which causes so much disability has not received consideration. This omission may of course have been purposeful so as to leave this large subject of disability following childbirth for a future congress. The prevention of other common gynaecological disorders such as fibromyomata and endometriosis, however, is given a place, and the influence of heredity in genital tumour production and the relationship between infection and genital tumours is considered.

A small but important section is devoted to the surgical and radiological treatment of genital cancer; and indeed it would be remarkable if an international congress in gynaecology could take place without mention of this very important subject.

In obstetrics the theme is the protection of the child during pregnancy and delivery. After a short section on the general aspects of the relation between the foetus and the mother there is a section devoted to abortion and premature labour. Nutrition during pregnancy, toxaemia of pregnancy and diabetes in pregnancy are also discussed. Blood incompatibility is also considered and then the question of intra-uterine infection of the child. Foetal anoxia is considered, and then obstetric trauma in the newborn.

Finally there is a section on the organization and teaching of prophylaxis in gynaecology and obstetrics. Each contribution is summarized in French and English as well as the parent language. The volume represents a comprehensive international forum of opinion and it is to be hoped that a similar volume may soon be published containing the 147 free communications which were also delivered during this congress. The publishers are to be congratulated on the production of this volume containing, as it does, contributions in five languages, from so many authors. The editors and their staff of translators and proof readers have performed a difficult task with commendable success.

"Practical Obstetric Problems." By IAN DONALD, *M.B.E.*, M.D., M.R.C.O.G., Regius Professor of Midwifery, University of Glasgow. Pp. xii+578. Lloyd-Luke, London, 1955. Price 45*s*.

IN his preface the author wonders what drives men to write a textbook, and he adds that in his case it was the persuasiveness of his publisher. A more satisfying answer lies in the opening sentence of the preface—"The art of teaching is the art of sharing enthusiasm." The good clinical teacher is perforce something of an exhibitionist as well as an enthusiast, calling at times on hyperbole or irony in order to drive home his lesson. All these characteristics are manifest in this book which is likely to become the standby of the obstetric practitioner and especially of the aspirant for higher degrees, for it presents a well-balanced account of modern obstetric practice.

The author has omitted the "inevitable dreary irrelevance of such matters as ovulation, menstruation, conception, infertility, diagnosis of pregnancy and early development of the ovum", in order that the size of the book might be, as the production and price are, exemplary. This does not mean that theory is eschewed; rather is it given full, and in places rather weighty, discussion. Nevertheless, the author's strong point is his practical approach to the clinical problem as it presents itself to the attendant. This is well exemplified in the chapters on the management of ante-partum and post-partum bleeding. Indeed all the practical aspects of abnormal or potentially abnormal midwifery are amply covered. Thus, for instance, a chapter is devoted to consideration of the elderly primigravida, the grande multipara and the "bad obstetric history".

There are contributed chapters on malpresentations (G. W. Garland), relief of pain (Hilda Roberts), the toxaemias of pregnancy (H. M. Carey) and the use and misuse of antibiotics (W. Hayes). The last two deserve special commendation, for Carey's chapter is a model of concise if a trifle dogmatic information, while Hayes has contributed a most excellent and practical section which will fascinate as well as instruct.

After this meed of well justified praise, what can the reviewer criticize? The pleasure of reading is occasionally marred by an inappropriate colloquialism and by the overuse of "of course". The illustrations are numbered separately for each chapter, which is a little confusing. The scope of domiciliary midwifery might have been more

sharply delineated. Otherwise, criticism can be directed only at points of opinion. Is abortion most common at the times of suppressed periods? Is there really no place for trial labour in elderly primigravidae, or for the use of pitocin in the treatment of concealed accidental haemorrhage? Is it wise or kind to discontinue general anaesthesia after delivery of the first twin rather than proceed at once with the second delivery? Is it good practice to defer catheterization for retention after delivery for up to 20 hours. Some might consider that the safety value of intact membranes and the dire significance of the passage of meconium in head presentations are both a little exaggerated. The only notable omissions are an account of that most disconcerting complication, the perineal haematoma, and a warning of the importance of catheterization after forceps delivery and the detailing of the steps to be taken if the urine is blood-stained.

All these, however, are but minor blemishes and are more than outweighed by positive virtues. The oft-repeated inaccuracies of the past are discarded and the unproved innovations of the present are not overrated. The attitude to X-ray pelvimetry is rational and balanced. The major importance of bed-rest for the cardiac patient at the 28th to 32nd week rather than during the last month of pregnancy is duly noted. The chapters on forceps and Caesarean section present sound statements of current views; the former is marked by an enthusiastic advocacy of Kielland's forceps, and the latter is marred only by the mis-spelling of the name of the late McIntosh Marshall. The section on the resuscitation of the newborn is admirable in content and the author's researches in this field are modestly appraised.

Above all, Professor Donald and his publishers are to be congratulated on the short period of gestation before delivery of this book, in which papers published as late as 1954 are noted. Altogether it is a fine book, well produced and attractively priced. If it is a sample of the obstetrics of the younger school of today, the high traditions of British midwifery are being well maintained.

"Normal Labor." By L. A. CALKINS, M.D., Ph.D., Professor of Obstetrics and Gynecology, University of Kansas, U.S.A. Pp. viii+129. Blackwell Scientific Publications, Oxford, 1955. Price 30*s*.

THIS small book is admittedly little more than an essay in which Dr. Calkins retails his attitude towards certain phenomena of normal labour. The substance, his views on the prediction of the length of labour and on the management of each stage, has appeared before; indeed, half of the total text comprises appendices which are reprints of 7 of his papers, published between 1928 and 1948. Accordingly this slim volume will probably be regarded in Britain as an expensive, and perhaps unnecessary, luxury, for its cost approximates that of many of our standard textbooks. Unfortunately most of the series of monographs to which this book belongs, the American Lectures in Gynecology and Obstetrics, seem unreasonably expensive by our standards.

This is not to disparage Dr. Calkin's views and arguments, for these are obviously the fruit of years of clinical research and close observation of the parturient woman. He corrects the false impression, not uncommonly held in Britain, that episiotomy, forceps delivery and caudal analgesia are routine procedures in all clinics in the U.S. Several telling points are made, notably on the possible blood-loss from episiotomy, and the measurement of the second stage not by time but by the number of contractions. On other points the views of the parous themselves might be of considerable interest. Most mothers would agree that after delivery "each patient should be allowed out of bed as soon as she is ready and able to do so". But there might be some strong comment on the paragraph which reads—"We have not yet reached the stage of having our patients walk from delivery room to their own rooms, but quite freely admit that we may be backward in this respect. We still walk from the bathroom after a bowel movement."

"Haemorrhage of Late Pregnancy." By JOHN S. FISH, M.D., F.A.C.S., Emory University School of Medicine, Atlanta, U.S.A. Pp. xii+180 with 22 figs. Blackwell Scientific Publications, Oxford, 1955. Price 40*s*.

IT is often stated that in some 40 to 50 per cent cases of ante-partum haemorrhage the cause remains undetermined. This is particularly likely when painless bleeding is treated expectantly and without recurrence, and the patient delivers at term normally and with no evidence of low implantation of the placenta. In this monograph in the American Lectures in Gynecology and Obstetrics series, Dr. Fish acts as spokesman for his group who, headed by Dr. R. A. Bartholomew, maintain that the commonest cause of bleeding in the last trimester is rupture of the marginal sinus of the placenta (40 per cent), with placenta praevia next in frequency (30 per cent), and with abruptio placentae occurring much less often (10 per cent). Moreover they believe that even in placenta praevia the major site of bleeding is the disrupted marginal sinus. It is disappointing, therefore, to find in the text no direct reference to the report by Hamilton and Boyd in this country in 1951 that the marginal sinus is a far from constant anatomical structure.

Nevertheless Dr. Fish has produced a well-written book, strong in cogent arguments and supported by excellent illustrations. His prime purpose has been to provide facts and theories to support the contention of his group, but in the process he has written an admirable survey of the whole subject of ante-partum haemorrhage, dealing with anatomy and histology as well as clinical features. In diagnosis, vaginal examination, properly timed, is the key; he doubts whether the form of treatment in painless bleeding can be decided on the abdominal findings alone or with the help of radiology—a view with which there may be some disagreement. In treatment the emphasis is on conservatism, even to the point that hydrostatic bags are mentioned, albeit without enthusiasm. The effects of the various types of ante-partum bleeding on the third and fourth stages of labour are discussed in detail.

Whether Dr. Fish has proved his point is for the individual reader to decide—but only if he is willing to review his own cases in the prescribed manner and assess his findings. If such a trial does nothing more than lead

the obstetrician to examine the delivered placenta, both naked-eye and microscopically, with greater care, the author will probably regard his efforts as well-directed. On one small point we may learn something from Atlanta—every expectant mother there is requested to send during her pregnancy at least one donor to the local blood bank.

"Antenatal and Postnatal Care." By F. J. BROWNE and J. C. MCCLURE BROWNE. Eighth edition. Pp. viii+672, with 94 illustrations. J. & A. Churchill, Ltd., London, 1955. Price 37*s.* 6*d.*

THE fact that this book has reached its 8th edition bears testimony to its popularity but a critical survey of the present edition suggests that it would, with benefit, be pruned of many unimportant details and out of date facts.

The book is easy to read. Some chapters, such as that on diseases of the urinary tract, are very well done. The pathological descriptions are excellent. The commonly employed biological and biochemical tests are clearly described. No student could wish for a more extensive bibliography. Unfortunately, the book has many faults, which detract from its merits.

The title is misleading, there being no mention of labour, and yet the book contains very much more relating to this subject than to postnatal care which is compressed into a mere 15 pages. A small paragraph disposes of the care of the lying-in patient. Nothing is said of infant-feeding. Indeed, the only conditions mentioned in connection with babies are congenital malformations (and their inheritance) and haemolytic disease, no less than two chapters being devoted to them.

The chapter on diseases of the circulatory system starts off with a good account of heart disease, yet ends with needlessly long descriptions of extreme rarities, viz., rupture of aneurysms of the splenic and renal arteries, and curiously enough no mention of the infinitely more common subarachnoid haemorrhage. There are many similar instances of lack of proportion and balance. Thus only five lines are devoted to the treatment of incomplete abortion, and five to that of septic abortion! Torsion of the uterus, endometritis and cord traction, all admitted to be rare causes of accidental haemorrhage, are dealt with in some detail before toxaemia is mentioned. It is illogical to discuss the management of a twin labour and not that of a breech or face presentation. It is doubtful if as much as $\frac{1}{2}$ c.cm. of pituitary extract should be given to stimulate pains to deliver the second twin. Such contradictory statements as "vaginal douching at any stage of pregnancy is dangerous and should be avoided unless ordered by a doctor" are not very helpful.

In the preface the authors claim to have done much pruning, but more remains to be done. Why, after they have dealt quite competently, and in no little detail, with the routine antenatal examination of the patient, should it be necessary to call upon Mr. Wrigley to write another four pages to "still further elaborate those ideas"? An effort should be made to omit or severely prune obsolescent matter, e.g., the long description of the external pelvic measurements. Similarly, two outdated papers (both published in 1939) form the basis of discussion of the section on pneumonia. Surely the antibiotics have altered the whole picture.

The chapter by Dr. Grantly Dick Read could be considerably reduced without losing any of its value. It contains many dubious statements, such as "few cases of toxaemia or hypertension have been recorded in women of emotional stability" or "in a series of nearly 500 consecutive cases conducted with attention to the mental as well as the physical aspect of childbirth, over 98 per cent of the women . . . breast-fed them successfully", when reference to Read's original article shows the truth to be that 15 per cent were classified as "breast-feeding—poor" and 26 per cent as "breast-feeding—fair".

It will thus be seen that much alteration of this book is necessary before it can be confidently recommended to the undergraduate or doctor.

REVIEW OF CURRENT LITERATURE

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PHYSIOLOGY

94. Cyclic Changes of Cervical Mucus.

By B. E. URDAN and A. M. KURZON. *Obstet. Gynec.*, **5**, 3–12, Jan. 1955. 8 figs. 13 refs.

Crystallization in the cervical mucus is significant because it is initiated only by oestrogen stimulation. It can be studied by placing cervical mucus on a clean glass slide which, having been dried, is examined under the low-power microscope. Seventy-nine patients were studied by the authors. They found that crystallization occurred in the proliferative phase of the menstrual cycle and at the time of ovulation. With the production of progesterone by the corpus luteum there was a disintegration and disappearance of the crystals in 24–72 hours and a replacement by a cellular pattern which persisted until the onset of menstruation. This change marked the time of ovulation. Pregnancy could be presumed when the cellular phase persisted for an unusual length of time.

The menopause was differentiated from the cellular pattern of a normal cycle by the presence of a loose formation of squamous cells in the cervical mucus.

J. G. Dumoulin

95. Urinary Excretion of Oestrogens During the Menstrual Cycle.

By J. B. BROWN. *Lancet*, **1**, 320–323. Feb. 12, 1955. 8 figs. 1 table. 11 refs.

The author records his results of using a new chemical method for estimating the urinary excretion of oestriol, oestrone and oestradiol–17β during 10 normal menstrual cycles. He points out that results obtained by biologically measuring the oestrogens excreted have little quantitative significance. Twenty-four-hour urine specimens were collected daily throughout the whole menstrual cycle. The amounts of the three oestrogens excreted were found to rise and fall together. During the first week the excretion is lowest and begins to rise about the 7th day to gradually reach a peak ("ovulation-peak") some 14 days before the onset of the next period. The peak is followed by a sudden decrease, to be followed by a second maximum ("luteal maximum") on about the 21st day. A second decrease occurs before the onset of menstruation but the lowest levels often occur several days after the onset of menstruation.

H. H. Fouracre Barns

96. Simultaneous Registration of Uterine Contractions, Tubal Contractions and the Oscillations of the Utero-tubal Insufflator. (Registro simultaneo de las contracciones uterinas, de las tuberias y de las ossilaciones de la persuflacion uteró-tubaria.)

By A. STÁBILE, R. C. BARCIA and H. ALVAREZ. *Obstet. Ginec. lat.-amer.*, **12**, 281–285. July 1954. 10 refs. 4 illus.

Referring to an earlier paper by one of the authors (Stábile), it is stated that the oscillations shown in a tracing of tubal insufflation by the Rubin apparatus are due to contractions in the interstitial part of the Fallopian tube, which acts as a sphincter, and not to contractions in any other part.

This publication describes the method by which the above statement can be demonstrated by three simultaneous tracings taken of muscular contractions in the interstitial and the isthmial parts of the Fallopian tube, and the oscillations due to pressure variations in the cervical canula during a Rubin test.

The technique described consisted of inserting Caldeyro Barcia y Alvarez's intramuscular micro-balloon (containing 0·02 ml. of water), at laparotomy for non-gynaecological conditions, into the musculature of the interstitial and isthmial parts of the Fallopian tube of cases previously proved by insufflation to have normal patency. The Fallopian tube on the opposite side was clamped during the demonstration.

Tracings were then taken from the pressure variations in the two intramuscular micro-balloons at the same time as a tracing from the Rubin apparatus whilst in action. By comparing the three simultaneous recordings, it was observed that tracings from the interstitial part of the Fallopian tube and Rubin apparatus coincided, but the tracing from the isthmial part of the tube was different.

By inserting an intramuscular micro-balloon into the fundus of the uterus as well, the rhythm of the muscular contractions at this site was shown to be different from that at the cornua; the authors thereby conclude that different parts of the uterus contract with different rhythms.

John F. Foulkes

PREGNANCY

97. **Effective Circulation of the Uterine Wall in Late Pregnancy Measured with ^{24}NaCl.**

By N. Morris, S. B. Osborne and H. D. Wright. *Lancet*, **1**, 323–325. Feb. 12, 1955. 1 table. 17 refs.

The authors have investigated the clearance rate of radio-sodium injected directly into the wall of the pregnant uterus. The same site was selected in 48 pregnant women. Twenty were normal cases between the 34th week and term; 10 had mild pre-eclamptic toxaemia between the 34th week and term; 8 had severe pre-eclampsia between the 30th and 39th weeks of pregnancy; and 10 had twin pregnancies between the 32nd week and term. The observations made show that the clearance rate in a twin pregnancy was decreased as compared with the single pregnancy; and was about half the normal in mild and only a quarter in severe cases of pre-eclampsia. They suggest that the pre-eclamptic syndrome becomes manifest at a time when the demands of the foetus and the trophoblast exceed the supply that can be maintained by the maternal circulation; that the trophoblastic anoxaemia may prove to be an important factor or even the "trigger mechanism" which determines the onset of pre-eclampsia. In 5 cases of pre-eclampsia they found the clearance rate increased when the patient was effectively treated with hypotensive drugs.

[This suggests that the hypertension causes the diminished uterine circulation rather than a deficient uterine circulation causing the hypertension (pre-eclampsia).]

H. H. Fouracre Barns

98. **Carbohydrate Tolerance in Pregnancy.**

By J. F. C. C. Cobley and H. O. Lancaster. *Med. J. Aust.*, **1**, 171–175. Feb. 5, 1955. 23 refs.

Remarking that there is little information in the literature on the changes in carbohydrate metabolism during pregnancy, the authors present the results of glucose tolerance tests, performed at monthly intervals throughout pregnancy on 158 pregnant women.

The mean fasting blood sugar level is quite constant over the months of pregnancy. The mean blood glucose level ½ an hour after the ingestion of glucose is constant over the months of pregnancy and is about 125 mg. of glucose per 100 ml. of blood. At 1 hour the figure is about 130, at 1½ hours about 118, at 2 hours about 106, at 2½ hours about 93, and at 3 hours about 83.

The authors' findings strongly suggest that carbohydrate tolerance does not alter during pregnancy. There is a slight delay in the return of the glucose tolerance curve to normal during pregnancy. This careful study of a large series has been checked statistically.

S. Devenish Meares

99. **Intrauterine Roentgenography as an Aid in Determining Foetal Age.**

By T. W. Adams. *Obstet. Gynec.*, **5**, 43–48. Jan. 1955. 6 refs.

Intra-uterine X-ray studies were made by the author in an attempt to determine the age of the foetus. Lateral views were taken at weekly intervals after the estimated 32nd week of gestation in 64 cases. The appearance of ossification in the distal epiphysis of the femur was sought, since this is usually present by the 34th to 37th week of pregnancy. Thirty-nine cases of diabetes were included in this series.

In 27 cases in which pre- and post-delivery X-rays were taken, the author claims an accuracy in interpretation of 89 per cent. He believes the method is useful in determining the time during pregnancy when the induction of premature birth may be undertaken with a comparatively good outlook for foetal survival.

J. G. Dumoulin

100. **Blood Replacement in Obstetrics and Gynecology.**

By J. L. Gaspar. *West. J. Surg. Obstet. Gynec.*, **63**, 71–79. Feb. 1955. 10 refs.

Current methods of storing blood are reviewed and it is stressed that, except in cases of acute haemorrhage, blood transfusion should not be used as a method of treating anaemia which can be corrected by the administration of iron, liver, etc. The author advocates transfusion of the pregnant patient near term or pre-operatively when the haemoglobin concentration is 9 g. or less (60 per cent Haldane). The anaemias of infection are probably better treated by other means (there are no useful leucocytes in stored blood) but transfusion may be indicated in haemolytic or aplastic anaemias, purpura and leukaemia. Care should be taken to minimize blood-loss at delivery but, if blood transfusion is required, the blood should be given under pressure and the amount given assessed from the patient's response. The importance of

accurate cross-matching is stressed as is also the time required for this essential step in transfusion technique.

[This is a very sensible paper and the author's words echo those of DeLee: "The woman's own blood is best."]

D. C. A. Bevis

101. **The Use of the Magnesium Ion in the Management of Eclamptogenic Toxemias.**

By J. G. PRITCHARD. *Surg. Gynec. Obstet.*, **100**, 131–140. Feb. 1955. 7 figs. 15 refs.

Since 1951 in the Western Reserve University School of Medicine and University Hospitals of Cleveland, Ohio, a study of the advantages of magnesium sulphate used alone as a therapeutic agent for the management of cases of toxaemia of pregnancy has been coupled with a more fundamental investigation of some of the pharmacological properties of the magnesium ion.

Patients actively convulsing with eclampsia received intravenously 4 g. of magnesium sulphate in a 20 per cent solution in a period of 4–5 minutes. This was immediately followed by an intramuscular injection of 10 g. of magnesium sulphate in a 50 per cent solution, one half the total volume deep in each buttock. Then every 4 hours as long as the patellar reflex was present and the 4-hour urine output was 100 ml. or more, 5 g. in a 50 per cent solution were injected intramuscularly. This schedule was adhered to until delivery and usually for 24 hours afterwards. In cases of pre-eclampsia the intravenous injection was omitted. All doses of magnesium sulphate refer to USP $MgSO_4 7H_2O$ and not to anhydrous $MgSO_4$ which contains twice as much magnesium as the USP salt.

During the 3-year period 211 patients with pre-eclampsia or eclampsia were treated with magnesium sulphate and it proved to be a potent and safe drug for inhibiting eclamptic convulsions. No patient in the pre-eclamptic group convulsed after magnesium sulphate therapy was instituted and no patient with eclampsia had a further convulsion. There was 1 maternal death from cerebral haemorrhage on the fourth day post-partum. There were 221 infants delivered from the 211 toxaemic patients. The uncorrected perinatal mortality was 10 per cent.

The mechanism by which the magnesium ion so efficiently controls the convulsions was not elicited. It was found to have no significant hypotensive action either in eclampsia and pre-eclampsia or in other hypertensive states unassociated with pregnancy.

Magnesium sulphate given orally was absorbed poorly and produced no significant change in the plasma magnesium concentration. With the intravenous injections of 4 g. of magnesium sulphate there was an initial peak plasma concentration followed at first by a rapid fall, and then by a slower rate of decline. Following intramuscular injection there was an initial 60–90 minutes lag before there was significant elevation of the plasma magnesium concentration. The continued intramuscular injection of a 5 g. dose at 4-hourly intervals resulted in a nearly uniform plasma magnesium concentration ranging from 3·5 to 7 milli-equivalents per litre.

Following the administration of magnesium sulphate the rise in plasma magnesium in the foetus equalled that of the mother but no significant depression resulted and breathing and crying times were normal. The increase in amniotic fluid magnesium level occurred more slowly than in foetal plasma and was more variable.

Parenterally administered magnesium produced a slight average decrease in renal plasma flow and glomerular filtration rate and a transient increase in sodium excretion. It was found to have no effect on uterine contractions.

The distribution of parenterally injected magnesium prior to its excretion was investigated by determining the apparent volume of distribution of intravenously administered magnesium. It was found that both in humans and in dogs immediately after injection the magnesium space was not much greater than the inulin space but that the magnesium space, at first quite rapidly and then more slowly, increased to become in 24 hours about double the inulin space. The fate of the magnesium after leaving the extra-cellular phase prior to excretion was not discovered.

Close observation of the patellar reflex before repeating injections was found to be of great value in avoiding the development of magnesium intoxication. The patellar reflex disappeared with plasma magnesium concentration of 7–10 milli-equivalents per litre and loss of the reflex always preceded respiratory depression.

John P. Erskine

102. **Pharmacological Hibernation in the Anaesthetic Treatment of Eclampsia.** (Il trattamento anestesiologico dell'eclampsia gravidica mediante l'ibernazione farmacologico.)

By C. PEZZOLI. *Riv. Ostet. Ginec. prat.*, **36**, 497–503. Oct. 1954. 25 refs.

Seven eclamptic women were treated as follows: continuous oxygen by inhalation; 50 mg. promethazine intramuscularly; 100 mg. chlorpromazine, 50 mg. pethidine, 40 ml. magnesium sulphate (percentage not stated) in 500 ml. 5 per cent dextrose solution by intravenous drip. Procaine 0·6 g. in 250 ml. synthetic plasma was added to the drip for 2 of the patients—1 of whom had absent foetal heart sounds and 1 of whom had already been delivered. The infusion was repeated at intervals of 12 hours.

In all instances fits were controlled within 15 minutes to ½ hour. The patients came out of coma and slept lightly but could be roused easily. The blood pressure fell to within normal or nearly normal limits. Urinary output rose in 24 hours. All the women survived.

Of the 6 gravid women, 4 were delivered of live babies, 1 spontaneously, 1 following pitocin stimulation, 1 after surgical induction and 1 by Caesarean section; the other 2 had stillbirths.

The author considers these results are satisfactory and justify further trial. He subscribes to the belief that chlorpromazine and promethazine are ganglioplegic agents and safe for mother and child. Since this treatment is symptomatic, he does not think it would be wise to allow pregnancy to continue indefinitely.

[The use of terms such as hibernation, ganglioplegic and anaesthetic is misleading.]

M. Caturani

103. Simultaneous Placenta Praevia and Placenta Accreta.

By S. L. ISRAEL, A. SIEGEL and A. RUBENSTONE. *Obstet. Gynec.*, **5**, 27–31. Jan. 1955. 6 refs.

Although only 30 cases have been reported of the simultaneous occurrence of placenta praevia and placenta accreta, the authors believe that the combination is not as rare as this fact suggests. It may account for post-partum haemorrhage in cases of placenta praevia. The safest treatment would seem to be the radical one of Caesarean hysterectomy which was the treatment adopted in the case report which this paper presents. During the course of the Caesarean section the authors attempted a manual removal of the placenta and found that tags of myometrium were being removed with portions of torn placenta. Haemorrhage was severe necessitating total hysterectomy. This was performed with unaccustomed rapidity. *J. G. Dumoulin*

104. Iron Deficiency in Pregnancy.

By M. FISHER and R. BIGGS. *Brit. med. J.*, **1**, 385–386. Feb. 12, 1955. 3 figs. 12 refs.

The authors, from the Radcliffe Infirmary and the Health Department, Oxford, investigated the prevention of "physiological anaemia" of pregnancy by the administration of iron. The investigation was carried out in 138 patients booked for domiciliary delivery and attending two local health antenatal clinics between January, 1951 and April, 1953. Haemoglobin estimations were made at the first attendance, at 28 weeks, at 38 weeks, and at the postnatal examination 6 weeks after delivery. The iron preparations used were "fersolate" tablets—9 gr. of ferrous sulphate daily, or, if the patient complained of digestive disturbances, "ferro-redoxon"—6·12 gr. of ferrous sulphate with 150 mg. of ascorbic acid daily. Owing to incomplete records some patients were finally excluded, leaving 104 remaining patients.

Twelve patients failed to respond to iron therapy and were separated as a group of non-responders in whom the haemoglobin level was still below 85 per cent at 38 weeks. The responders were sub-divided according to their initial haemoglobin. Where that was above 90 per cent, there was little change in the level throughout. Where it was below 90 per cent, the level rose steeply with iron administration, and was around 98 per cent at 38 weeks, and maintained for some weeks after delivery.

In the small group of non-responders only was there the downward trend described as "physiological anaemia" of pregnancy. These patients, however, showed a sharp rise after delivery, possibly due to better utilization of iron.

The authors make a plea for giving iron as a routine to all pregnant women, and feel that it would ensure a high level of haemoglobin at term in almost 90 per cent of cases. *Eileen Wilson*

105. Acute Renal Failure as an Obstetric Complication.

By K. P. RUSSELL, J. F. MAHARRY and J. W. STEHLY. *J. Amer. med. Ass.*, **157**, 15–20. Jan. 1, 1955. 6 figs. 11 refs.

This study from the Los Angeles County Hospital gives details of 34 patients in whom acute renal failure occurred as an obstetric complication, and the aetiology, clinical course and management are discussed. In the type of case considered the mechanism was regarded either as nephrotoxic or circulatory (renal ischaemia), but many other complex contributing factors are described. In a very large proportion of cases in the first trimester the primary cause of renal failure was septic induced abortion, and some of the cases were associated with infection by *Clostridium perfringens*. Towards the end of pregnancy abruptio placentae was the commonest cause.

The average duration of anuria or oliguria in the 26 patients who recovered was 8·3 days. The level of nitrogenous products in the blood only gives a gross index of the degree of renal damage and is of no great value in prognosis. The average non-protein nitrogen level of the 26 patients who recovered was 195 mg. per 100 ml., whereas the average level in the 8 who died was 147 mg. per 100 ml. Hypochromic microcytic anaemia often seemed to develop some time after the acute precipitating episode and appeared to be due to a combination of haemolytic reaction and toxic depression of erythropoiesis. Treatment was by careful fluid restriction, control of electrolyte balance, antibiotics in the abortion cases, and small blood transfusions if necessary. Dialyzing procedures were used in 7 cases. The overall mortality in the series was 23·5 per cent, and the renal damage in 2 of the patients who died is clearly shown by photomicrographs. *D. W. James*

106. Practical Points Relating to Rupture of the Uterus.

By J. K. FEENEY. *J. Irish med. Ass.*, **35**, 371–375. Dec. 1954.

Section I. Coincidental intra-partum rupture of the lower uterine segment Caesarean scar and of the urinary bladder, with the notes of two cases.

Two examples of this serious complication of pregnancy caused the author to consider carefully the anatomical relationship between uterus and bladder and certain points in the technique of lower segment Caesarean section.

In both cases a previous lower segment scar ruptured transversely and downwards; the bladder, in each case, showed an extensive transverse and vertical rupture, corresponding in shape and extent to the uterine laceration. Neither patient had had pyrexia following the previous Caesarean section.

In Dr. Feeney's opinion, trauma caused by downward displacement of the bladder by gauze dissection is likely to result in fixation of the bladder to the front of the lower uterine segment during the convalescent period. Violent rupture of both organs is likely to occur if the uterine scar begins to tear in a subsequent pregnancy or labour.

At one time the author believed that it was important to make the uterine incision well below the level of the utero-vesical fold of peritoneum; he is now convinced that it is possible to make an adequate incision in the lower segment, when the patient is in labour, without vigorous displacement of the bladder.

Section II. Some recent experiences in the Coombe Hospital.

In the past 5 years there have been 17 cases of rupture or perforation of the uterus in association with pregnancy at the Coombe Hospital; 10 of the cases were emergencies. It is interesting to note that the single maternal death occurred in a case of incomplete rupture. Dr. Feeney gives details of the 17 cases. Twelve important points in regard to the diagnosis and management of ruptured uterus are set out in the paper (readers are referred to the original).

Section III. Vaginal delivery after Caesarean section.

Over the past 5 years in the hospital, 100 women who had had a previous Caesarean section were allowed to come into labour. The indications for the previous Caesarean sections are enumerated. Eighty-five of the 100 women were delivered vaginally without serious complication; 13 of the remainder were treated by Caesarean section and 2 patients had Caesarean hysterectomies.

Although the author believes in the relative safety of controlled vaginal delivery after previous Caesarean section, he stresses the need for caution in the management of these cases. Hospital delivery is essential and the instruments for laparotomy should be kept ready for immediate use from the onset of labour.

J. K. Russell

107. **Fatal Air-Embolism Associated with Ruptured Uterus.**

By W. F. Scrimgeour and J. E. Carrick. *Lancet*, **1**, 485–487. Mar. 5, 1955. 8 refs.

The authors report 2 cases of fatal air-embolism associated with ruptured uterus. Both cases occurred immediately after delivery. The rupture was at the level of the internal os of the cervix. Clinically there was a sudden onset of a raised pulse rate, reduced blood pressure, air hunger and pallor. Both patients also complained of severe backache and 1 had cyanosis instead of pallor. The authors draw attention to the close similarity to so-called obstetric shock occurring after labour and not associated with severe haemorrhage. They suggest that some of these cases may be explained by minor degrees of air-embolism insufficient to produce death.

H. H. Fouracre Barns

108. **Anxiety in Pregnancy.**

By P. A. Reynolds. *West. J. Surg. Obstet. Gynec.*, **63**, 88–94. Feb. 1955.

Childbirth without fear or pain rarely occurs and the author stresses that anxiety should be treated with every technique available. Education can do much to improve the well-being of the patient but often the physician must explain the ambivalent feelings towards pregnancy and her near relatives. In these cases relief is often gained by getting the patient to express her true feeling about being pregnant. The patient must also be encouraged to regard herself as an individual, without reference to standards of behaviour in pregnancy and labour as imposed by her acquaintances. The author points out that commendable as they are, lectures, books and classes on child care often increase instead of diminishing anxiety.

D. C. A. Bevis

LABOUR

109. **Significance of Initial Condition of Cervix Uteri to Subsequent Course of Labour.**

By D. P. Cocks. *Brit. med. J.*, **1**, 327–328. Feb. 5, 1955. 8 refs.

An investigation of the relationship between the condition of the cervix at the time of surgical induction and the course of labour was undertaken in 133 cases at University College Hospital. Most of the women were primigravidae at or near term and cases of disproportion were excluded.

Five types of cervix are described. Types 1 and 2 are soft and admit a finger ("ripe"), the canal effacing in type 1 but still long in type 2. Types 3 and 4 are firm ("unripe"), the external os being closed in type 3 and the internal os rigid in type 4. Cervical anomalies, e.g., the pin-hole os, are grouped together as type 5. In any of these types there may be a sacral os with anterior sacculation and this was noted in 34 cases.

Results showed that the average induction-interval and length of labour were significantly less in the 89 cases of ripe cervix without a sacral os than in the 9 cases where it was considered unripe but normal in position. Only 1 type 5 cervix was encountered and Caesarean section was indicated after 9 hours in labour with a pin-hole os.

The 34 cases with a sacral os had a greatly prolonged induction-delivery-interval compared with the rest of the series, the latent period being particularly increased.

The rates of forceps delivery and Caesarean section showed a higher incidence of interference in the unripe os compared with the ripe types of cervix and the section rate was particularly high when the os was sacral, for there was a marked tendency to prolonged labour in these cases.

Careful assessment of the cervix before induction may be very helpful in deciding the management of a case. If it is unfavourable and delivery urgent, Caesarean section may be a better alternative. If there is less hurry, the membranes may be swept through a sacral os and this or a pitocin drip may produce a more favourable cervix 2 days later.

[There is no mention of whether the type of membrane rupture was constant. In the only case reported in detail, a Drew-Smythe catheter was used.]

Doreen Daley

110. **The Use of Continuous Intravenous Oxytocin in Obstetrics.**

By J. M. Holmes. *Lancet*, **2**, 1191–1193. Dec. 11, 1954. 5 figs. 9 refs.

The author records that the response of the human uterus to oxytocin varies with the dose and also with the irritability of the uterus. Using a Lôrand tocograph, uterine response may be shown to be completely tetanic; or less completely tetanic with irregular contractions; or normal with intermittent contractions; or completely

absent. A method of intravenous administration of oxytocin in high dilution is then described. Major cephalopelvic disproportion is first excluded. One unit of oxytocin is added to 1 pint of normal saline which is given to the patient as an intravenous drip. The rate of administration is regulated to produce intermittent uterine contractions lasting 60–90 seconds and recurring every 4–6 minutes. Once the desired response is obtained the same rate of administration can be continued throughout the first stage of labour, the rate being reduced by a half during the second and third stages.

He reports the results in 27 patients treated in this manner, the indications being induction for toxaemia (5), hypotonic uterine inertia (3), and premature rupture of membranes (5), among others. From his observations the author states that the drip may be used to promote labour at all stages of pregnancy, in cases of premature rupture of membranes or where surgical induction has failed, and particularly where induction is necessary in the presence of prematurity, death *in utero*, carneous mole, vaginal sepsis and where the presenting part is not engaged. It is contra-indicated in cases of hypertonic uterine inertia, as uterine tetanus may result in cases of major cephalopelvic disproportion, and in the presence of foetal distress or placenta praevia.

H. H. Fouracre Barns

ANAESTHESIA

111. **Spinal Analgesia with Piridocaine Hydrochloride for Cesarean and Vaginal Deliveries.**

By B. A. GREENE and M. GOLDSMITH. *Surg. Gynec., Obstet.*, **100**, 88–90. Jan. 1955. 11 refs.

Previous workers have been impressed by the insignificant degree of motor paralysis during spinal anaesthesia with piridocaine hydrochloride. Spinal analgesia without thoraco-lumbar motor paralysis is especially valuable to the parturient as it provides a safeguard against the anaesthetic hazards of a full stomach, obesity and a large intra-abdominal tumour. Furthermore, profound abdominal motor paralysis is unnecessary in vaginal or abdominal delivery.

The desired level of analgesia for either vaginal or abdominal delivery is the 9th thoracic dermatome. A vasopressor drug is injected 10 minutes before anaesthesia in all but hypertensive patients. The dose of piridocaine hydrochloride is 25 to 30 mg. The solvent is 2·5 to 3 ml. of 5–10 per cent glucose. Lumbar puncture may be performed with the patient sitting or horizontal. After injection the patient assumes the supine horizontal position with the head flexed.

Effective analgesia is provided for Caesarean section lasting 1 hour or vaginal delivery within 2 hours. Analgesia can be prolonged by up to 120 minutes by substituting, for an equal volume of glucose solvent, 1 ml. (50 mg.) of ephedrine sulphate or 0·6 ml. of 1 : 1,000 solution or epinephrine hydrochloride.

Spinal analgesia with piridocaine has been utilized for 225 Caesarean sections and in 3,400 cases for labour and vaginal delivery. The patient can bear down forcefully, cough vigorously and breathe normally.

No death or serious neurological complication has been attributed to the method or drug. Spinal headache occurred in only 0·4 per cent.

John P. Erskine

MATERNAL MORBIDITY

112. **Post-pregnancy Osteoporosis.**

By B. E. C. NORDIN and A. ROPER. *Lancet*, **1**, 431-434. Feb. 26, 1955. 3 figs. 2 tables. 12 refs.

The authors record their observations on 4 cases of osteoporosis seen post-partum. They point out that generalized rarefaction of the skeleton is usually due to osteomalacia or osteoporosis. While osteomalacia is usually due to steatorrhoea in Western Europe, in the East, where dietary Vitamin D is barely adequate, it is commonly precipitated by the demands of pregnancy and lactation. In this condition there is the pathognomonic radiological feature of the Milkman fracture and characteristic biochemical changes of reduction in the product of the serum-calcium and serum-phosphate concentrations and a rise in the serum alkaline phosphatase. Osteoporosis, on the other hand, is primarily a disorder of the protein matrix of the bone and there are no biochemical changes in the serum. It may result from malnutrition, thyrotoxicosis, Cushing's syndrome, acromegaly, scurvy or without obvious cause, usually in the elderly. In the 4 patients recorded, the symptoms of lumbar backache and pains in both thighs occurred during or within a few months of delivery. All patients breast fed their babes for at least 3 months. There was limitation of flexion of the spine and tenderness over the lower dorsal and upper lumbar spinous processes. X-ray of the spine showed extensive rarefaction with biconcave deformities (codfish vertebrae) and crush fractures. The serum calcium and phosphate levels were normal. Bone biopsies taken from the iliac crest showed thin fractured trabeculae in 2 cases of recent origin. The authors draw attention to the fact that there was nothing in the patient's histories to suggest inadequate intake of calcium or Vitamin D. They suspect that there may be some connexion between the condition and childbearing and suggest that it may prove to be related to the increase in adreno-cortical activity during pregnancy similar to that in Cushing's syndrome.

H. H. Fouracre Barns

INFANT

113. **Alkali Reserve and Chlorides in Arterial and Venous Cord Blood.**

By N. HALLMAN, K. ÖSTERLUND and P. VARA. *Ann. chir., gynaec. fenn.*, **43**, 216–220. 1954. 10 refs.

This is an investigation of plasma alkali reserve and chlorides in arterial and venous cord blood immediately after birth and in maternal blood during the second stage of labour; also of chloride content of erythrocytes. The number of cases is not quoted but the following results were found. The venous alkali reserve was slightly lower than normal (24·6±0·4 mEq/l) and higher than in arterial blood, the difference being 2·5±0·3 mEq/l. Plasma chlorides were slightly lower in venous than

arterial blood with the reverse true for the chloride content of the erythrocytes. The maternal alkali reserve was much lower (18·6±0·5 mEq/l). The chloride content of the erythrocytes was higher in cord blood but no difference was found with regard to plasma chlorides.

D. M. Sheppard

114. **Care of Premature.** (L'assistenza al prematuro.) By P. BATTARINO. *Minerva ginec., Torino*, **6**, 127–128. Oct. 31, 1954.

Close collaboration is nowadays necessary, and is usually available, between the obstetrician and the paediatrician in the supervising of these infants if improvement in their chances of healthy survival is to be obtained. The author distinguishes between "immatures" (infants otherwise healthy who weigh below 2,500 g., say 5½ lb.) and "prematures", a category which includes besides immatures various abnormal or pathological infants with the same weight qualification.

The vital functions less well secured in immatures are those of respiration, circulation, and heat regulation. Assistance at birth should be limited to episiotomy, and forceps delivery should be avoided as the risks of damage to the delicate foetal head of immatures outweigh any possible advantages of speed. Similarly, anaesthesia should be avoided or limited to local block.

Reliable apparatuses are now available to provide germ-free air regulated as regards temperature and humidity, thereby minimizing the perils of environment. The article passes over the question of feeding, merely requiring small and frequent feeds of human milk whether of its own mother or of a milk bank. Additions of vitamins, antibiotics, and administration of blood, infusions, etc., may be needed, and it is in deciding on such measures that the cooperation of a paediatrician may be most helpful. *W. C. Spackman*

115. **Rapid Rh-Typing. A "Sandwich" Technique.** By F. STRATTON. *Brit. med. J.*, **1**, 201–203, Jan. 22, 1955. 3 refs.

A Simple Method of Rh-Typing. By P. W. HARVEY. *Brit. med. J.*, **1**, 203–205. Jan. 22, 1955. 4 refs.

Two methods of Rh-typing are described. Stratton's is a rapid slide "sandwich" test and can be performed in 10 minutes at 37° C. It is intended for use in emergency transfusion.

Harvey advises his method for routine use as a time-saving but reliable procedure. The patient's cells are centrifuged with anti-D serum in a thermostatically controlled jacket at 37° C.

[The texts give clear and detailed instructions for the performance of these tests. The slide test is likely to be of great use to an obstetrician who cannot obtain a 24-hour pathological service.] *Doreen Daley*

116. **The Foetal and Neonatal Wastage due to Sensitisation by the Rh Factor.** By G. A. KELSALL and G. H. VOS. *Med. J. Aust.*, **1**, 261–263. Feb. 19, 1955. 4 refs.

From a study of 260 immunized Rh-negative mothers, who had a total of 1,009 foetuses, the figures for miscarriages, stillbirths and neonatal deaths have been obtained.

From this comparatively small series the authors consider that iso-immunization is unlikely to be responsible for many abortions. Stillbirths are unlikely to occur when the titre of the maternal antiglobulins (indirect Coombs' test) is low, such as below 1 : 128.

The percentage of infants alive and well 14 days after delivery in the affected series was 72·15 while 92·3 per cent of the controls survived. *S. Devenish Meares*

117. **Exchange Transfusion as a Means of Removing Bilirubin in Haemolytic Disease of the Newborn.** By G. H. LATHE. *Brit. med. J.*, **1**, 192–196. Jan. 22, 1955. 14 refs.

Brain damage occurs with varying frequency in haemolytic disease of the newborn and ordinary exchange transfusion is not entirely effective in preventing it. Kernicterus is associated with great excess of the indirect-reacting plasma pigment, bilirubin, and this may also reach high levels in premature infants without haemolytic disease.

A detailed study of the pigment changes was undertaken on infants with haemolytic disease at Hammersmith Hospital. It appears that high levels of bilirubin do not often continue for more than 48 hours and are maximal on about the third day of life. Efforts to remove the excess pigment by exchange transfusion revealed the interesting points that in a large transfusion more bilirubin can be removed than the baby's blood volume is calculated to contain at the beginning of the procedure but the replacement does not lower the plasma pigment as much as expected from the amount of blood exchanged. It seems that there is continued passage of pigment from the tissues but a drop of 30–50 per cent in its concentration can be expected from exchange transfusion and this, repeated when necessary, should keep the bilirubin level below 20 mg. per cent, which seems to be a critical level if kernicterus is to be avoided. The number of transfusions needed will depend on the speed with which the liver develops the capacity to excrete bilirubin and this function is slow to develop in the premature infant, which may also be sensitive to levels less than 20 mg. per cent. These aspects of the problem must be considered when premature delivery is being considered.

Blood for exchange transfusion should be as fresh as possible, for the greater liability to early breakdown of preserved blood cells will inevitably increase the infant's accumulation of bilirubin.

Occasionally there is a marked rise of direct-reacting bile pigments and this may cause biliary obstruction with thrombi. Further work is needed to establish whether or not these pigments are damaging to the brain.

Doreen Daley

GYNAECOLOGY

118. **The Metabolic Concept of Gynecological Care.** By H. G. HAMILTON. *West. J. Surg. Obstet. Gynec.*, **63**, 56–59. Feb. 1955.

The author points out that the peak of hormonal efficiency is reached between the ages of 18 and 25 and that after this there is a gradual waning until the menopause is reached. The aim of the gynaecologist should be to maintain the changing state of fluid and electrolyte balance, iron metabolism and calcium maintenance that the waning brings about. Small doses of thyroid, oestrogens and androgens can do much to improve the physical well-being of patients and attention to diet and treatment with ammonium chloride can correct aberrant water metabolism, a common condition at ovulation and menstruation. *D. C. A. Bevis*

119. **Electronic Studies in Obstetrics and Gynecology.** By K. J. KARNAKY. *Obstet. Gynec.*, **5**, 93–101. Jan. 1955. 11 figs.

The author reports on the use of the Brown potentiometer electronic recording machine in determining the pH of the vagina in different conditions.

The vaginal pH in normal healthy persons varies from 3·5 to 4·2. Within 4 hours after a douche or coitus the pH increases to 4·5–4·7. Mild types of vaginal infections produce a pH of 4·8 or 4·9. A reading of 5 differentiates the mild from the chronic infections, and at this degree of acidity a serious glycogen depletion of the vaginal epithelium begins. Although there is more lactic acid in the vagina of the pregnant patient, the pH does not vary from that of the non-pregnant. In trichomonas vaginitis the vaginal pH is about 5·5, but may be 8·5 in the most acute cases. The author believes that the itching in this condition derives from products resulting from incomplete glycogen metabolism.

Monilia infection may be found at any pH of the vagina between 5·5 and 8·5. Treatment by alkaline tablets is therefore not justified. The pH in cervical ectropion will vary according to the amount of alkaline secretion produced.

In the normal senile vagina the pH varies between 6·4 and 8·0, and this may rise further in infected cases.

Temperature studies were also carried out. Vaginal douches as hot as the patient could stand did not cause a rise in temperature of either the cervix or the uterus, and only a slight rise in that of the rectum, and are of little value in pelvic infections. *J. G. Dumoulin*

120. **Recurrent Genital and Oral Ulceration with Associated Eye Lesions (Behcet's Syndrome).** By D. I. PHILLIPS and J. S. SCOTT. *Lancet*, **1**, 366–371. Feb. 19, 1955. 6 figs. 37 refs.

The authors record their observations of 10 cases of recurrent genital and oral ulceration associated with lesions of the anterior chamber of the eye. All the patients were in the reproduction period of life. The lesions tended to heal and recur spontaneously. Pain notably preceded the appearance of the ulcers and dyspareunia was associated with the genital ulcers, which occurred on the vulva mainly. Healing was associated with considerable scarring. The oral lesions were similar to but smaller than the genital ulcers. The eye lesions began as superficial inflammation proceeding in 3 patients to iridocyclitis, one of which ended in complete blindness. Other lesions which may occur in addition to the triad are monarticular arthritis, various C.N.S. symptoms and signs, and skin lesions resembling erythema nodosum on the extremities. Treatment has been ineffective in the past but the authors record satisfactory and encouraging response to cortisone and corticotrophin in 4 cases. It is pointed out that diagnosis of the syndrome was made when 2 of the 3 main features were present. This was on account of the fact that some time may elapse between the initial symptoms and the development of the full triad. A serious aspect of the syndrome is the central nervous system involvement which may mimic disseminated sclerosis or suggest an intra-cranial neoplasm. Cases have been recorded where such involvement was the immediate cause of death. The aetiology of the syndrome is unknown. Most of the cases occur in young adults (including males) resident in the Eastern Mediterranean area. The genital and oral lesions of Behcet's syndrome are identical with those of ulcus vulvae acutum, periadenitis mucosa necrotica recurrens and aphthous mucosal ulceration, and the picture is further complicated by the occurrence of several other syndromes of unknown aetiology and displaying similar behaviour patterns such as Reiter's disease and ectodermosis erosiva pluriorificalis. The authors conclude that the syndrome and the related syndromes may eventually fall into place among the collagen diseases.

H. H. Fouracre Barns

121. **Irregular Shedding of the Endometrium.** By M. THIERY. *Gynaecologia, Basel*, **139**, 1–24. Jan. 1955. 11 figs. 44 refs. [In English.]

This is a study of 22 cases of irregular shedding of the endometrium collected from a total series of 25 cases. The condition is defined as an abnormality of menstruation in which the endometrium shrinks, sheds, involutes and regenerates more slowly than normally, giving the clinical picture of prolonged and excessive menstrual bleeding.

In the present series it was estimated that the cases made up 10 to 17 per cent of cases of menorrhagia. The age of the patients in the series varied from 24 to 50. No definite relationship to childbearing was demonstrated though, in one-fourth of the cases, menorrhagia coincided with the first periods following abortion and parturition. Certain other common diseases were found in these patients but there was nothing to suggest a common aetiology. Fibroids, endometrial polypi and other lesions were found which might contribute to the bleeding. Blood dyscrasias and hypertension were not believed to be relevant to the condition. The menstrual cycle was essentially unchanged in length, though menstrual losses were increased in duration. Iron deficiency anaemia was common.

The histological picture is described together with the clinical features of 5 typical cases. The histological picture is of a contracted necrotic endometrium with round celled infiltration and interstitial haemorrhage. The endometrial glands vary in pattern but are often in the secretory phase but slit-like in shape. Degenerate pseudodecidual cells may be seen. The coiled arterioles of the endometrium show degeneration.

The aetiology of the condition is discussed and it is

decided that its true cause remains obscure. It has been suggested that delayed degeneration of the corpus luteum of menstruation may be responsible.

The diagnosis depends on a history of gradually increasing painless menorrhagia with no sign of organic disease. Curettings should be obtained during bleeding. The histological features seen in the endometrium are as follows: the appearance is that of late secretory endometrium, generally lacking its covering epithelium. The endometrium presents an irregular pattern with a combination of pre-menstrual, fragmented and involuting endometrium. Ascending pillars of predecidual cells surround the coiled arterioles which show fibro-elastic degeneration.

The treatment should consist initially of curettage which will, by itself, cure many cases. When curettage fails, the best treatment may be simple hysterectomy, or in women near the menopause artificial menopause with radium or X-rays.

Hormone therapy may be tried. Large doses of oestrogens may be used as a temporary uterine haemostatic. Progesterone has also been tried with the idea of causing a "hormonal curettage".

[This is a very good survey of an important condition and one which may elude diagnosis unless curettage is performed during a bleeding episode. Naturally gross pelvic pathology such as fibroids or even uterine malignancy must be excluded and hormone treatment should never be given in cases of uterine bleeding until the histological diagnosis of the cause has been established.]

Josephine Barnes

122. **The Menstrual Pattern in Hyperthyroidism and Subsequent Post-therapy Hypothyroidism.**

By R. C. Benson and M. E. Dailey. *Surg. Gynec. Obstet.*, **100**, 19–26. Jan. 1955. 6 figs. 7 refs.

With the intention of establishing the menstrual pattern during thyrotoxicosis and after specific therapy, the authors reviewed the clinical histories of 274 premenopausal patients with authenticated hyperthyroidism treated at the University of California Hospital during the past 15 years. The cases were divided into 3 categories:

1. 221 with toxic diffuse goitre, including Graves' disease;
2. 20 with toxic nodular goitre;
3. 33 with toxic recurrent goitre;

and they were then further subdivided according to the severity of the initial hyperthyroidism.

A critical review of the menstrual histories of the patients with mild toxic diffuse goitre revealed that 50 per cent had experienced a decrease in amount and duration of menstrual flow while only 5·7 per cent described an increase in bleeding. In the moderate cases a menstrual decrease occurred in 60 per cent, an increase in 3·4 per cent and in the patients with severe toxic diffuse goitre menstrual decrease occurred in 74 per cent and increase in 7 per cent.

Fourteen per cent of the 221 patients with toxic diffuse goitre noted the onset of toxic goitre at the time of a pregnancy.

Ten of the 33 patients with toxic recurrent goitre described a decrease of menstrual flow but none admitted an increase.

Thirteen of the 20 patients with toxic nodular goitre experienced oligomenorrhoea but none noted menorrhagia.

If all grades of severity of thyrotoxicosis in this series are combined, it becomes apparent that, if a change does occur in the menstrual pattern, it almost invariably consists of a suppression of the flow in association with oligomenorrhoea or amenorrhoea. No cases of amenorrhoea due to hyperthyroidism were recorded in patients who did not also manifest exophthalmos.

Clinical hypothyroidism occurred in 31 (14 per cent) of the total number of patients with toxic goitre who were treated. Eighteen of these noted menorrhagia or polymenorrhoea and in none did the menstrual flow decrease during the time of abnormally low thyroid function. Treatment with desiccated thyroid generally led to a return to normal menstruation within 2 months.

The authors discuss pituitary-thyroid-ovarian relationship with regard to menstruation and describe hormonal and nutritional mechanisms which may be responsible for the menstrual changes in toxic goitre and in hypothyroidism.

John P. Erskine

123. **Treatment of Anovular Menstruation.** (Sulla terapia della mestruazione anovulare secondo Maurizio.)

By N. Pasetto. *Minerva ginec., Torino*, **6**, 721–725. Nov. 15, 1954. 4 figs. 36 refs.

Opinion is sharply divided as to the possibility of inducing regular ovulation in established cases of anovular menstruation, and this is not surprising in view of the great complexity of the physiology involved. Moreover, the methods of treatment which might, or are claimed to, have effect are each subject to so many variants that the issue becomes even more confused.

Firstly there are certain mechanical steps which might influence the "genito-pituitary reflex", such as dilatation or splitting of the cervix, and infiltrations of the cervical ganglia. These measures are not discussed, and are evidently (and rightly?) not given much credit. Many authorities reject such measures for the purpose under discussion.

Medical measures of treatment are (*a*) direct, by applying physiological and gonadotrophic stimulants, or (*b*) indirect, which endeavour to correct a supposed disequilibrium of the endocrine balance, involving the thyroid, suprarenal and pancreas (insulin).

The author has treated a series of cases by the direct method, essentially a treatment with gonadotrophin, but this requires some elaboration. Serum gonadotrophin (derived from pregnant mares' blood) and/or chorionic gonadotrophin (from the urine of pregnant women) can be used. There are numerous investigators who uphold each method and an equal number who failed to confirm their claims.

Maurizio's method, propounded by the author, uses a combination of both forms of gonadotrophin and adds

testosterone. The cases are divided into two groups, those showing hypo- or hyper-folliculin characters, and the treatment is different for the two groups, but all are treated in addition with liver extract and vitamin B complex on general grounds.

A. Hypo-folliculin cases. He gives serum gonadotrophin, 1,000 I.U. on the 6th, 9th, and 12th days of the cycle (or 500 I.U. each day from 6th to 12th) followed by 1,000 I.U. chorionic gonadotrophin on 13th day and 2,000 I.U. on 14th and 15th days. Diethylstilboestrol, 0·2 mg., daily from 6th to 11th days and 0·3 mg. on 12th to 14th days. Methyl-testosterone on 10th, 12th, and 14th days. [One cannot help feeling that the return to "eye of newt and toe of frog" is not far off.]

B. Hyper-folliculin cases. Serum gonadotrophin and oestrogens are omitted. Chorionic gonadotrophin is given as before and progesterone 5 mg. on 9th, 11th, and 13th days alternating with 5 mg. methyl-testosterone on 10th, 12th, and 14th days.

This scheme of treatment is carried out for 3 consecutive months. Results claimed: of 19 cases treated on these lines, 63·2 per cent gave a positive test for pregnanediol in their urine and a third of these (i.e., 21 per cent of all cases treated) became pregnant within 6 months and 26 per cent within a year.

Finally, the question of production of antihormones is mentioned, it being stated that this contingency does not arise for chorionic (human) gonadotrophin, and where serum gonadotrophin is used "it need not be taken into account".

W. C. Spackman

124. **Anovulatory Cycle and Sterility.** (Ciclo anovulatorio y esterilidad.)

By N. ARENAS and A. E. BETTINOTTI. *Obstet. Ginec. lat.-amer.*, **12**, 385–389. Aug. 1954. 2 figs. 17 refs.

The authors draw attention to the variation in the statistics of absence of ovulation in sterile women, as given by different writers. They suggest that this is due to the variety of methods used for diagnosis and the fact that authors differ in the manner of expressing their statistics.

After quoting the figures given by various writers, the authors indicate their preference for the endometrial biopsy as being the most satisfactory method of determining ovulation, but, because this is a tiresome procedure for the patient to experience repeatedly, they resort to the temperature chart method as a means of observing patients over a long period, but nevertheless warn the reader that biopsies must also be taken in sterility investigations to exclude primary endometrial defects.

The authors express great confidence in the therapeutic value of thyroid extract and of irradiation to ovaries and pituitary to stimulate ovulation.

Finally, they discuss the relationship of such symptoms as dysmenorrhoea to ovulation, and, in a series of 27 such cases, found failure of ovulation in 9 patients. Similar relationships are also reported on such vague subjects as frigidity, orgasm, etc., but the numbers are too small to have any real clinical value.

John F. Foulkes

125. **The Intra-uterine Pessary of Petit Lefour in the Treatment of Sterility.** (Sul meccanismo d'azione del pessario endouterino nella terapia della sterilita.)

By P. QUAINI. *Minerva ginec., Torino.* **6**, 728–735. Nov. 15, 1954. 34 refs.

The indications for this pessary are stated to be in the treatment of congenital anteflexion, stenosis of the cervical canal whether structural or functional, uterine hypoplasia, dysmenorrhoea and sterility, and good results are claimed in some of these conditions.

The author treated 78 cases of sterility with this instrument. Of the 57 he was able to follow up, 29 became pregnant in from 2 to 42 months. A high proportion, however, as might have been expected, suffered in their pregnancies from threatened or actual abortion.

Many of the cases were submitted to other lines of treatment at the same time. Altogether, a convincing case has not been made out.

W. C. Spackman

126. **The Treatment of Pelvic Inflammatory Disease with Local Antibiotics, and their Relationship to Sterility.** (Tratamiento de los procesos inflamatorios polnianos por los antibióticos locales y su relación con la esterilidad.)

By N. ARENAS and P. L. M. PASI. *Obstet. Ginec. lat.-amer.*, **12**, 450–452. Sept. 1954. 8 refs.

The authors are so impressed with the clinical results of injecting penicillin into acutely inflamed pelvic tissues, that they have made this a routine procedure in their hospital practice in Chile.

In adnexal inflammatory disease they claim that pain and pyrexia disappear within 3–4 days, and inflammation completely resolves in 15–21 days: the more acute the inflammation, the sooner does it resolve.

After mentioning such procedures as injecting penicillin into the Pouch of Douglas and penicillin with 1 per cent novocaine into the parametrium, the authors refer to the technique employed by other writers using similar modes of treatment. They all assert that the patient stands a better chance of conceiving after pelvic inflammatory disease when this route of antibiotic therapy is used.

Detailed records of 2 cases are given: 1 patient received daily injections of 200,000 units of penicillin with 1 per cent novocaine into the parametrium on each side for 3 days as well as the application of antibiotics to the cervix, and short wave diathermy for 15 days. The patient subsequently conceived. The second case reported in detail received similar therapy and conceived also at a later date.

A survey of 34 cases, who had received the same treatment, was carried out, but only 15 could be traced (and the clinical records of these are given in brief). Of the 6 who were liable to conceive because of age and circumstances, 3 were found to be pregnant.

The authors conclude that, if their method of treatment is given promptly before adhesions have had time to form, fertility after pelvic inflammatory disease is unimpaired.

John F. Foulkes

127. **Trichomonas Vaginalis Infections. Use of Carlendacide in Treatment.**

By C. H. Davis. *West. J. Surg. Obstet. Gynec.*, **63**, 53–55. Feb. 1955.

Carlendacide is a mixture of polyoxyethylene nonyl phenol, sodium ethylene diamine tetra-acetate and sodium dioctyl sulphosuccinate that has been found to be more effective than other detergents in killing trichomonads. 1 ml. of the preparation is added to 250 ml. water and is stable on storage. The vagina is swabbed with this 1 : 250 solution and after 3–4 minutes the vagina is dried; a minimum of 6 treatments over 2–3 weeks is recommended. Non-pregnant patients are also advised to douche morning and night with 1 teaspoonful (3·5 ml.) in 1 quart (1 litre) of warm water, the douching continuing over the menses. The husbands are instructed to wash the glans penis daily with 1 : 500 solution and always after coitus. It is suggested that a jelly containing 1 per cent of the mixture may prove more effective than douching.

D. C. A. Bevis

128. **Genital Tuberculosis.**

By R. K. Plant. *West. J. Surg. Obstet. Gynec.*, **63**, 81–86. Feb. 1955. 2 refs.

The author reviews recent views on pelvic tuberculosis and states that it is always secondary to a focus elsewhere in the body and should be suspected if salpingitis occurs in the absence of gonorrhoeal or postabortal infection. The diagnosis should be obvious in a child or virgin. Masses are only mildly tender and often indefinite in outline. If the endometrium is involved the degree of menstrual upset depends on the extent of the disease and may be minimal. Involvement of the cervix produces dull yellowish-grey tubercles or a granulomatous growth like carcinoma. He reviews 31 patients under his care, 24 of whom had symptoms referable to the pelvis, 23 showed abnormal pelvic findings. Washing out the uterine contents at the menses and culturing the blood is considered a better procedure than a diagnostic curettage, but only 8 cultures were positive out of 26 although many of the patients were examined when they were not bleeding. Half the patients were nulliparous. Twelve patients were operated upon, 6 for conditions other than tuberculosis. Subsequent to admission 4 patients had pregnancies, one having an ectopic. There were no deaths in the series. The author considers that treatment should be primarily medical but does not give any details of treatment.

D. C. A. Bevis

129. **Myomata of the Female External Genitalia.** (Über die Myome der äusseren Genitalien der Frau.)

By P. A. Järvinen, O. Kinnunen and C. von Numers. *Ann. chir., gynaec. fenn.*, **43**, 221–228. 1954. 3 figs. 10 refs.

This is a short discussion on aetiology, frequency, symptoms and diagnosis of myomata of vulva and vagina with 4 case reports. Two cases were of vulval myomata (labium majus) and 2 were of vaginal myomata (anterior wall). All patients had uterine myomata present or had had operative treatment for them. The vulval tumours were small and only found by accident, whereas the vaginal tumours gave rise to symptoms. All were removed by enucleation and were fibromyomata on histological section.

D. M. Sheppard

130. **Concurrent Morbid Conditions Found in Uteri Removed for Non-malignant Affections.** (Sulle lesioni cervicale ed endometriali in uteri asportate per affezioni benigne del corpo.)

By U. Narducci. *Minerva ginec., Torino*, **6**, 767–775. Nov. 30, 1954. 7 figs. 40 refs.

Cancer developing in the cervix subsequent to subtotal hysterectomy is well known and is regarded as carrying a very high mortality rate. There is, however, much to be said for not performing a total hysterectomy where the cervix appears normal and healthy especially in the younger patients.

The author submitted to minute microscopical examination 140 uteri removed by total hysterectomy for non-malignant indications. Original diagnoses were fibroids, fibrosis, metritis, etc., and in none were there any suspicions, either from the anamnesis or the pre-operative clinical examination, of possible cancer. The average age of the women was 42·33 years.

Cervix. In 2 cases out of the 140, aged 38 and 40, carcinoma in the pre-invasive stage (intra-epithelial or stage 0) was found. Admittedly this stage can exist for many years before the basal membrane is pierced.

In 1 case, aged 43, an early invasive cancer was found by microscopic section, not demonstrable by clinical methods.

In 1 case, aged 49, an adenocarcinoma in the cervical canal was found.

In addition, abnormal or atypical but non-malignant epithelium was found in 94 cases out of 140.

Endometrium. Normal endometrium either in the proliferative or secretory phase was found in 71 cases. Of the remaining 69, 8 showed a "precancerous" endometrium, a cystic hyperplasia with irregularly proliferated and occluded glands but no invasive characters. Their average age was 39 years. The rest were labelled hyperplastic.

W. C. Spackman

131. **The "Suspicious" Smear in Gynaecological Cytology.** (Der "verdächtige" Ausstrich in der gynäkologischen Zytologie.)

By P. Stoll, L. Riehm and H. G. Bach. *Gynaecologia, Basel*, **139**, 39–50. Jan. 1955. 1 fig. 13 refs.

The fate of 425 patients with a "suspicious" vaginal smear has been followed. These came from a series of 5,619 patients examined during 3 years, making thus 7·6 per cent of the total series.

Of the suspicious smears, 54·1 per cent were subsequently proved not to have cancer while 26·6 per cent had cancer. Of the 76 cancers of the cervix 9 were preclinical and would not have been detected without cytological examination.

Josephine Barnes

132. **Cytological Diagnosis of Uterine Neoplasms.** (Resultati di 4 anni di dépistage delle neoplasie uterine col metodo citologico.)

By E. Guidici. *Minerva ginec., Torino*, **6**, 817–818. Dec. 15, 1954.

The Varese Hospital reports the results of 4-years work from examining 1,417 women attending the Women's Department or the laboratory connected with it. Of this number 14 were excluded from the report as being already under radiological treatment and 76 others in whom clinical signs of neoplastic lesions were apparent.

Two slides for cytological study were made from each patient, 1 from the cervix and 1 by aspiration from the canal. Fixing and staining as well as assessing the findings followed Ayre's scheme (*Amer. J. Obstet. Gynec.*, 1946, **51**, 743), and in doubtful cases a further slide was made after an interval. Thus from 1,417 cases 4,239 slides were examined. Of these, 810 presented clinically no evidence of uterine disease, in 368 there was irregular bleeding or cervicitis, and in 239 the condition of erosion or ectropion was seen.

A diagnosis of cancer or pre-cancerous neoplasia was made in 133 cases, confirmed by biopsy in 121 and reported negative by biopsy in 12. These cases represented 10 in the endometrium, 22 in the cervical canal, 82 on the portio and 2 of the vulva. There were no false negatives and less than 1 per cent false positives. Actual cancers detected were 14 cervical, 10 endometrial and 2 of the vulva. Success and usefulness of the method depends equally on careful taking of the slides in the clinic and an expert cytologist.

W. C. Spackman

133. **Growth Characteristics in Tissue Cultures of Controversial Lesions of the Uterine Cervix.**

By J. G. Moore. *West. J. Surg. Obstet. Gynec.*, **63**, 1–8. Jan. 1955. 8 figs. 8 refs.

The author describes the results of investigations carried out at the University of California. Tissue obtained by cervical biopsy was minutely subdivided and explanted under aseptic conditions into a thin film of clotted plasma; this was then incubated in a mixture of placental cord serum, chick embryo extract and physiological saline. Twenty-seven cervical carcinomas, 8 non-pregnant normal cervices, 8 pregnant normal cervices and 8 possible carcinomas *in situ* (Stage 0) were studied. It was found that most of the frankly malignant tissue grew easily and tissue from carcinoma *in situ* grew almost as rapidly but normal tissue did not grow at all. The author does not recommend tissue culture as a means of diagnosis as it is tedious, expensive and requires considerable patience, moreover, not all malignancies grow easily. From the behaviour of carcinoma *in situ*, however, he advises that this condition should be treated by the standard methods for cervical cancer rather than risk inadequate therapy under the impression that it is only minimal invasion.

D. C. A. Bevis

134. **Virilism due to Ovarian Arrhenoblastoma.**

By P. R. C. Evans and R. O. Jones. *Lancet*, **1**, 436–437. Feb. 26, 1955. 2 figs. 13 refs.

The authors record a case of ovarian arrhenoblastoma occurring in a young girl of 15 years. The menarche had occurred at the age of 13 with normal periods for 1 year. For 6 months prior to being seen she had complete amenorrhoea. During the same time she noticed that her singing voice began to break. As no abnormality in the pelvis could be detected, and the urinary excretion of 17-ketosteroids was within normal limits, she was kept under observation. During the subsequent 5 months there was increasing hirsutism, deepening of the voice and slight enlargement of the clitoris. At this stage enlargement of the left uterine appendages was felt. Removal of a left ovarian arrhenoblastoma caused the periods to recommence 1 month after operation. The hirsutism had disappeared when seen 1 year after operation but the voice was still low pitched 2 years after operation.

H. H. Fouracre Barns

135. **Sarcoma and Sarcoma-like Proliferations of the Endometrial Stroma. I. A Clinicopathologic Study of 19 Mesodermal Mixed Tumors.**

By R. E. Symmonds and M. B. Dockerty. *Surg. Gynec. Obstet.*, **100**, 232–239. Feb. 1955. 10 figs. 24 refs.

This is a study of 19 mesodermal mixed tumours encountered among 43 cases of various types of endometrial sarcoma seen at the Mayo Clinic between 1910 and 1952. Three of the tumours involved the vagina and affected infants of 12, 15 and 24 months of age. The one cervical primary growth occurred in a 17-year old girl. The average age of patients with corporeal tumours was 61 years.

The symptoms and signs did not differ significantly from those of other malignant growths of the uterus. The tumours tended to be globular and polypoid with a smooth glistening outer surface. The cut surfaces were pinkish white and the tissue was of brain-like consistency.

The bulk of each tumour was composed of highly malignant fibro-cellular or fibro-myxomatous tissue. The presence within the tumours of malignant tissue which was dysontogenic as regards the endometrium was a *sine qua non* for diagnosis. This heterotopic tissue took the form of malignant striated muscle, cartilage and bone. An epithelial component existed in 14 of the 19 tumours. In 7 it resembled endometrial or endocervical glandular inclusions while in the remainder it was frankly adenocarcinomatous.

In the majority of cases treatment consisted of total hysterectomy and bilateral salpingo-oöphorectomy. A number of these received post-operative roentgen therapy but its value is questioned by the authors. Four of the patients have survived from 9 to 19 years following operation. This represents a comparatively good salvage rate as only 3 other cases have been reported in the literature in which patients have survived more than 5 years.

John P. Erskine

136. **A Case of Endometriosis in the Groin.** (Ein Fall von Endometriose der Leistenbeuge.)

By M. Roukkala. *Ann. chir., gynaec. fenn.*, **43**, 260–264. 1954. 1 fig. 8 refs.

This is a description of a small tumour in the left inguinal region which became swollen and tender during menstruation. On investigation it was found to be attached to the round ligament in the inguinal canal and,

on section after excision, was found to be composed of endometriotic tissue. There is a discussion of the theories of origin of endometriosis in this situation.

D. M. Sheppard

OPERATIONS

137. **Culdoscopy.**

By W. T. Black and H. B. Turner. *West. J. Surg. Obstet. Gynec.*, **63**, 49–52. Feb. 1955. 3 figs. 5 refs.

Inspection of the pelvic viscera through a puncture wound in the pouch of Douglas may sometimes be very helpful in diagnosis. The procedure should be carried out in an operating theatre if possible but local anaesthesia is often all that is required. It should not be performed indiscriminately but only in cases where there is doubt whether surgery is indicated. Success depends on the care with which cases are selected and the experience of the operator.

The author, at the University of Tennessee, has carried out the procedure on 60 patients and 45 of these were saved from an unnecessary operation. The main use of the technique appears to be in the diagnosis of unruptured tubal pregnancy.

D. C. A. Bevis

138. **Transverse Low Abdominal Incision with Detachment of the Recti from the Pubes. Follow-up Study of Eight Hundred Cases.**

By L. S. Cherney. *J. Amer. med. Ass.*, **157**, 23–26. Jan. 1, 1955. 6 figs. 4 refs.

This incision offers many advantages in operative treatment, and the author has made a follow-up study of 800 cases from various sources and includes 130 personal cases from the University of California. The technique recommended begins with the usual curvilinear incision of the skin and rectus sheath. The lower flap of the rectus sheath is separated as far as the pubes and the recti are cut transversely at the exact insertion without leaving a cuff and are then reflected upwards. The inferior epigastric arteries may require ligation and the peritoneum is incised transversely one fingerbreadth above the bladder. In closing the incision there is no need to establish the original insertion of the recti into the pubes, and the recommended procedure is to pull the rectus tendons down gently and insert 5 mattress sutures into the lower flap of the rectus sheath at the level to which the recti reach without being forced.

The exposure gives an operative field which may be nearly twice as large as that afforded by the vertical incision. Post-operative hernia in the series from various hospitals was from 2 per cent to 11 per cent for all cases, but only from 0·5 per cent to 2 per cent in clean undrained wounds. Lighter anaesthesia was required, post-operative discomfort was less, and the cosmetic effect excellent. The incision combines the advantages of the Maylard-Bardenheuer and the Pfannenstiel incisions without the high incidence of post-operative hernia of the former and the limited exposure of the latter.

D. W. James

139. **Vaginal Hysterectomy. Individual Variations in Technique and End-Results.**

By A. L. Banks and R. N. Rutherford. *West. J. Surg. Obstet. Gynec.*, **63**, 23–30. Jan. 1955. 6 figs. 8 refs.

The results are presented of 120 operations carried out in a private hospital over a 3-year period to the end of 1953. Contra-indications to the vaginal route include the uterus being larger than a 16-week pregnancy, endometriosis, pelvic inflammatory disease, possible malignancy, an ovarian tumour larger than 3 cm. diameter and previous pelvic surgery. Detailed evaluation of the pelvic floor is carried out pre-operatively and a vaginal smear examined for malignancy and ovarian activity. Patients with atrophic vaginal mucosa are given oestrogen creams or pessaries and obese patients put on a reducing diet.

The cervical mucosa is divided all round at the level of the vaginal plications and the bladder pushed up with dry gauze; the pouch of Douglas is opened and the utero-sacral ligaments clamped and stitch-ligated, the suture ends being left as markers. The pelvis is now inspected and the uterus pulled backwards and downwards; the anterior cul de sac is opened under direct vision and the ovarian pedicles and round ligaments cut and double ligated with a haemostat on the second suture. This is repeated on the uterine vessels and cardinal ligaments and, after the uterus has been removed and examined, the peritoneal cavity is closed with a suture of No. 1 chromic catgut. If an enterocele is present it is now dealt with and cystocele corrected by a Kelly-type plication of the urethra. The cardinal ligaments are now sutured together to form a new apex for the vagina, the round ligaments and utero-sacral ligaments being tied to this. The vesico-vaginal fascia is then attached to the apex and the vaginal mucosa closed with No. 1 chromic catgut. Defects of the posterior vaginal wall are repaired by separating the posterior vaginal fascia from its midline raphe, a crown suture placed at the apex to grasp the levatores ani on either side, the levatores approximated with interrupted sutures and, finally, the vaginal mucosa closed and the perineum repaired. All patients have an indwelling catheter for as long as required and ambulation is insisted upon on the 2nd post-operative day.

There were no deaths in the series but 2 patients returned with bleeding from the posterior vaginal cuff 2 weeks post-operatively. Twenty-eight patients had slight pyrexia during the first 3 days but all were afebrile by the 7th day. The average stay in hospital is 5 days for the hysterectomy and if a repair is carried out, the stay is 7–10 days.

[This is a good account of the operation although the indications seem a little lax.] *D. C. A. Bevis*

UROLOGY

140. **Paraurethral Fixation for Stress Incontinence.**

By S. G. Berkow. *Obstet. Gynec.*, **5**, 74–80. Jan. 1955. 8 figs. 15 refs.

Since first describing the operation of paraurethral fixation for stress incontinence in 1941, the author has

improved it. He points out that the mechanism of urethral closure in the female includes a vascular element, a rich venous plexus situated in the loose areola tissue of the submucosa. This acts as a "washer", keeping the bladder watertight, although the musculo-fascial sphincters are the more important elements in urinary control. However, post-menopausal impairment of urinary control may be precipitated by decreased blood flow in the submucous venous plexus.

In the operation of paraurethral fixation the urethra is advanced, angulated and sutured under the clitoris. The entire elongated urethra is buttressed with musculofascial supporting tissues. Levator fibres and the triangular ligament are sutured under the lower third or half of the urethra. A second row of sutures unites the bulbocavernosus muscles under almost the whole length of the urethra.

The author discusses the indications and contraindications for this operative procedure, the technique of which he describes in detail, giving diagrams.

J. G. Dumoulin

141. **Cortisone and Adrenalectomy in Treatment of Sterility in Women with Adrenogenital Syndrome.**

By S. F. Wilhelm and R. G. Marks. *J. Urol.*, **73**, 17–24. Jan. 1955.

The histories of 3 patients are given:

The first, a woman of 28, had been married for 9 months and, despite a normal sex life, did not conceive. The patient was not obese but had a masculine appearance and there was an excess of hair on the face, chest and extremities. The urinary 17-ketosteroids were 28·3 mg.

Investigation revealed a hydronephrotic right kidney but there were no abnormal adrenal shadows. A nephropexy and partial right adrenalectomy were performed. On opening the peritoneum, it was found that the left ovary was atrophic and the right ovary cystic.

The patient became pregnant 2 months later and eventually gave birth to a normal boy. Unfortunately no ketosteroid estimation was done during pregnancy. A second conception took place a year later and 2 years after the birth of the second child the 17-ketosteroids were 26·1.

The second patient, aged 28, complained of sterility, hirsutism and scanty menses. She had gained 35 pounds in 2 years. The 17-ketosteroids were 55·9 mg. and laminographic X-rays showed a mass in the left adrenal. Left adrenalectomy was performed and a tumour which was an adenoma was discovered. One month later 17-ketosteroids were 1·2 mg. and the patient had become feminized. Pregnancy occurred and a normal child was born.

The third patient, aged 29, had menstrual irregularity for 2 years and complained of hirsutism and increasing obesity. The 17-ketosteroids were 71·3 mg. Tomographic X-rays revealed no abnormality in the adrenal area. This patient was treated with oral cortisone, 25 mg. per day, gradually increasing to 50 mg. a day. The obesity diminished and her periods become normal. The ketosteroids were reduced to 13·5 mg. Conception followed soon afterwards and the patient gave birth to a premature baby, weighing 2 pounds 6 ounces. The child died 3 days later. At autopsy subarachnoid haemorrhage and bilateral adrenal haemorrhage were found. The cortisone treatment for the mother was not held to be responsible for this.

The adrenogenital syndrome can be produced by: (1) Neoplasm; (2) adrenal hyperplasia; (3) excess of secretion without any demonstrable growth or histological changes.

Pyelography is useful in showing displacement downwards of the kidney in the case of tumour and perineal insufflation with tomographic X-rays can distinguish between a tumour and hyperplasia.

Cortisone in the presence of hyperplasia reduces the ketosteroid level, but no such effect is produced if a tumour is present.

J. H. Carver

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